On the Clinical Relationships of Multiple Pseudoneuromata with Cutaneous Pigmentation and Dermato-fibromata and the various other Manifestations grouped under the Heading of

GENERALISED NEUROFIBROMATOSIS.

Being a THESIS for the DEGREE of M.D., Edin.Univ.

BY

G E O R G E H E N R Y M A S S O N .

of Trinidad.

Paris.

During the Summer Session of 1895, I followed a course of Clinical Instruction at the Hotel-Dieu in this city, and from the abundance of good material produced by the different clinicians, my attention was greatly taken up with two cases of a remarkable disease, shown by Dr. Pierre Marie (who at that time was temporarily filling the place of Professor Germain Sée) in which the outstanding features were a combination of tumours of subcutaneous nerves, with diffuse pigmentation and multiple tumours of the skin.

On my return to Edinburgh at the end of the Session this interesting malady still continued to engage my attention, the more so, as on careful inquiry I found the English literature on the subject to be of the scantiest possible description.

I was determined, however, not to abandon the subject, and, later on, when it became possible for me to take another trip to Paris, I put myself in communication with Dr. Marie, who generously consented to allow me to study in his own wards at the Hospice de Bicêtre, one of the two cases I had previously seen

in 1895, the other having died in the interval.

The results of my personal observations, and of my inquiry into the general facts bearing upon the combination of symptoms I have referred to, are embodied in the following Thesis, which I beg to present to my Examiners in the hope that it may be deemed to have attained the standard required for the M.D. Degree.

GEORGE HENRY MASSON, M.B., C.M., (1895).
B.Sc., Dept. of Public Health (1896).

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Fig.I. Back view of the patient Flond. Tumors and pigmented spots on his body, but seen by looking sideways rather than down on the surface. The large obliquely directed patch in the right lumbar region is well seen.

The case which I beg to present to my examiners is that of Pierre Joseph Flond, admitted to the Hotel-Dieu on January 3rd 1893, and transferred to the Hospice de Bicêtre on February 11th 1896. He is an unmarried man, aet 56, and a carter by profession, though he had previously worked as a quarryman for thirteen years. He was born at Rancourt in the Department of the Somme, where his father died of Typhoid Fever when he (the patient) was young. His mother was blind at the time of her death. He had some brothers and sisters but they all died in infancy. He left his birthplace at an early age, and is unable to give any information about his relatives. He does not know whether his parents suffered from any skin disease, or had pigmentary spots or tumours about their body.

He suffered from Scarlet Fever when a child, and about the same period he had an Otitis of the left ear, which lasted for a long time, and left him completely deaf in that organ. At the age of 17 he had a bad whitlow on the index finger of the right hand, and at 18 had an attack of Typhoid Fever which kept

him in hospital for six months. On the day after his discharge symptoms of the disease again broke out and he was obliged to return for treatment. On this occasion he remained in hospital for a month and was then discharged completely cured.

He enlisted at 19, and performed several years of Military Service without ever being confined to bed. Two years before his present admission his toes were severely frostbitten, and his feet subsequently swelled to such a degree that he could not walk. Though he attributes his present illness to the frost-biting, he says that for a considerable time before this accident his general health was not very satisfactory. He was subject to headaches and giddy turns; he used to suffer also from pains all over his body, especially in his loins and in his limbs, but not particularly in the joints. The pains were rendered worse by muscular effort and he had great difficulty sometimes in loading and unloading his cart. From the time that his toes were frostbitten he says he noticed his general condition growing worse and worse until finally he was obliged to seek relief in a hospital.

He says also that although his feet were much swollen at the time, he walked without any assistance to the Hotel-Dieu, and that it was only while standing in the waiting room he felt his legs, as it were, give way, and he dropped to the floor. Since then he has not been able to walk unaided. About a week before admission he engaged a friend to trim his hair, and during the process, the latter observed several "fleshy lumps" on his scalp, and called his attention to them. Patient had not noticed them before, and they had never given him any pain or discomfort.

About a week afterwards similar lumps appeared on the anterior and posterior aspects of his trunk and also on his limbs. He also noticed that coincidently with the appearance of the lumps, the skin in various parts of his body became pigmented. He is positive that the tumours did not always exist on his body and that his could only have appeared shortly before they were first noticed. He is equally positive that the pigmentation appeared at the time indicated. He says, however, that for a considerable time before the multiple tumours appeared on his body, he

had suffered some inconvenience from a large lump which had made its appearance near his anus.

He says he has never suffered from any venereal disease, and that he has always been temperate. He rarely drank absinthe and never any brandy. He has never had any fits nor has he ever lost consciousness apart from the time when he had Typhoid Fever.

During the first six or eight months of his sojourn in the Hotel-Dieu, the patient never left his bed, owing to his inability to walk, but after this period his condition improved somewhat and he began to walk a little with the aid of a stick. He got on fairly well for a time and was even able to go up and down stairs, always however with the support of his stick. This went on for about six months, but by degrees he noticed that locomotion became more and more difficult, and finally he was obliged to take to his bed which he never leaves now except he is requested to do so for the purpose of observation. On these occasions patient is really able to walk a little, but he progresses slowly in a peculiar fashion of his own, by holding on to the back of a chair with

both hands, pushing the chair forwards and dragging his limbs after it. But even in this manner he only succeeds in covering very little ground. He is quickly seized with severe pains in his back, shooting from about the fifth dorsal vertebra down to the coccyx, and cramps in his legs, more especially in the left one, which compel him to return to his bed. He is unable to lift his feet from the floor when walking or above the plane of the bed when lying down; and any attempt to do so causes him intense pain. He is able to hold his hands up above his head, to put his arms out in a horizontal position and to perform various other movements without pain and without assistance.

Patient is a stunted, poorly developed, feebly muscular, aged looking man, of a rather dark complexion but not more so than one has a right to expect in a man who has always worked out of doors. He lies on his back all day, with his head and shoulders propped up with pillows and his lower limbs extended. His forehead is thrown into wrinkles and he looks straight in front of him into space with a fixed vacant gaze.

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Fig.II. Note the wasted gluteal muscles, and the general emaciated condition of the patient.

His thorax presents a peculiar appearance, due partly to a senile kyphosis and partly to a flattening of the front of the chest in the upper part and a bulging of the lower part in the antero-posterior and transverse axes. On both feet the metatarsus aon the tarsus and the toes flexed on the metatarsus. The right great toe is bent over the terminal phalanx of the first toe, and on the left side the first toe is flexed over th last phalanx of the great toe. Those flexions are to some extent overcome when the patient stands on the floor. His feet are cold and markedly cyanosed. His skin is moist and cool. His muscles are generally wasted, especially those of his limbs. His glutei have nearly completely disappeared and the skin over that region is thrown into a series of oblique rugae which are well seen in the accompanying photograph.

On stripping the patient one is at once struck with the remarkable rough and mottled appearance which his body presents, owing to the presence on its surface of large numbers of pigmentary spots and patches, and numerous small molluscum-like tumours.

Opposite Page 9.

Fig.III. To show the "major" tumor near the anus, and the pigmented patches on the buttocks.

On looking at him closely we observe these tumours to be even more numerous than at first supposed, there being a large number of very small ones which at first sight escape the observation. The chief sites of these growths are the trunk, both anteriorly and posteriorly and the scalp. They are not plentiful on the limbs. The distribution of the pigmentation coincides in a general way with that of the tumours except as regards the scalp, where the former is wanting. The tumours present for examination a great variety of features. They range in size from a pin's head to an acorn, the smaller ones being in the great majority. There is, however, in the perineum one tumour which is very much larger than all the rest. It is about the size and shape of a walnut and abuts the right lateral half of the anus. It is slightly constricted at the base, purplish in colour, with one or two brown pigmentary spots on its surface. It has a feel akin to that of a varicocele. The skin over the tumour is not materially altered from that of the rest of the part in which it occurs, neither is it adherent to the contents which can be freely

moved within the sac, except at the base, where the former appear to be fixed. This growth is not painful nor tender on pressure. On the opposite side of the anus there is another swelling about the size of an acorn. These are the two largest tumours to be seen on the surface of the body. The majority of the others are small and sessile, some are slightly pedundulated. Sometimes two small tumours are seen to coalesce to form a larger one. The skin over these growths is in most cases unaltered from that of the rest of the body. Sometimes it is pale, pinkish, purplish, or pigmented brown. Here and there a tumour may be seen growing from a pigmented spot; in other places the tumour is seen to be capped by a small brown spot as if the growth originated from the site of the spot and that the latter ceased growing or grew slowly while the former increased in bulk. Some of the tumours are oval, others more or less globular shiny and tense looking, with a sort of translucency, like a mistletoe berry, which frequently they resemble in size, shape and consistency. Others do not appear tense, but are slack looking and partially collapsed

as if the envelope were too large for the contents. Some again, are completely collapsed as if there were no contents at all, and the tumour consisted in a mere tag of skin projecting from the surface of the body. A good many of them had a broad base and are very flat; in order to make out their presence it is necessary to look along the skin and view them in profile instead of looking down upon them. These are in all cases better felt than seen. Sometimes a comedo with its little black head is seen on the tumour, at other times it is a hair or two that grow from the surface. For all the tumours this general fact is elicited, that they form part of, and are incorporated in the thickness of the skin, being displaced with the latter. To the touch some of them are tense and feel like a mistletoe berry or like a small grape. In others the feel is like that of a small grape that is over-ripe and the contents partly shrunken. In some again, a small nodule, harder than the rest of the general contents, is made out in the interior, but there are no fibrous partitions to be felt, the tumours are all unilocular. In a good few the feel

is like that of a mistletoe berry or of a grape from which the pulp has been expelled and nothing but the skin left. There are also very small milliary ones which merely give the skin over which they are situated a rough gritty feel; some of these disappear on pressure and return again when pressure is removed.

Further examination reveals the presence of tumours of sizes varying from a lentil to a small almond within the thickness of the skin. There is no external swelling to indicate their presence and they can only be made out by palpation. They are as a rule pretty mobile and can be made to slip under the finger in every direction except at one point, where they appear to be attached to the superficial layers of the cutis. Others of this variety cannot be moved about, and they feel merely as fixed nodules in the thickness of the skin.

The Pigment which is scattered over the trunk mainly, and on the limbs in a lesser degree, is for the most part in intimate association with the tumours, and takes the form of spots and patches. These are not raised from the surrounding surface, there is merely

a difference in coloration like the p atches on a pie-bald horse. The spots are far more numerous than the patches and give the skin a speckled appearance. They vary in colour from almost all shades of "coffee and milk" to a dark reddish brown. Some present a tawny yellow colour like that of fallen chesnut leaves in the Autumn; others are more of a reddish yellow and look like the freckles seen on the exposed parts of individuals who easily take on the sun in the Summer-time. In size some are mere dots without any appre-ciable dimensions, but the majority vary from one to two millimetres in diameter and rarely do they exceed three. The patches are few in number as compared with the spots. They are on the whole lighter in colour, though their shades vary. Their margins are always very sharply defined. In shape they may be oval or more or less rectangular, and they range in size from a haricot bean to an unshelled almond and sometimes larger. They are usually obliquely directed with their long axis in the transverse, and their short axis in the vertical plane of the body. The skin over which the spots and patches occur preserves

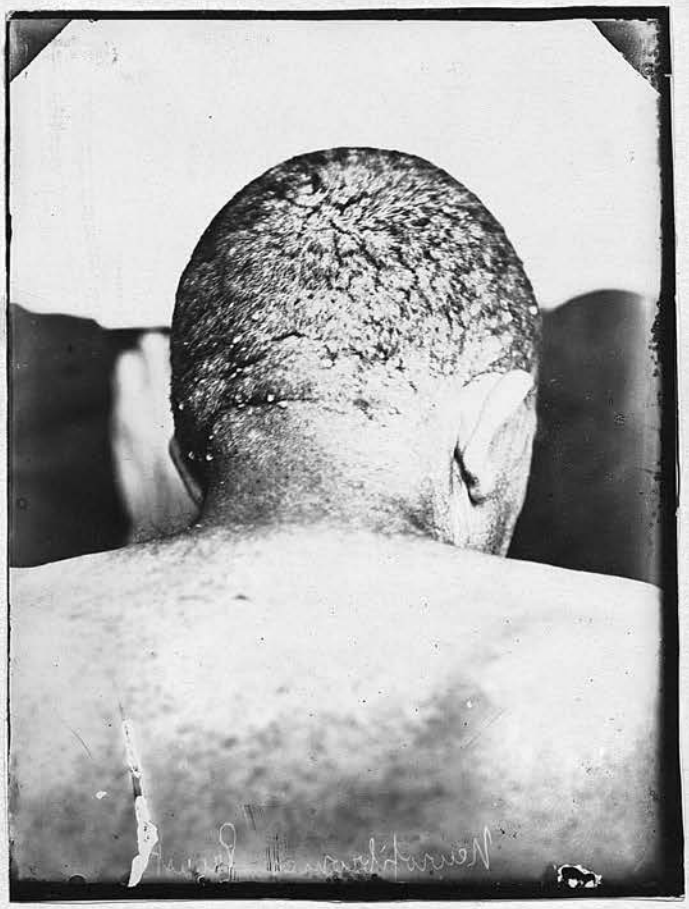

Fig.IV. Flond. To show the tumors on the scalp of the patient. Note their abundance in the occipital region.

the integrity of its texture and apart from the change of colour does not appear to differ in any way from that of the surrounding parts.

Besides the above there are a few small naevi varying in size from a pea to a threepenny bit. They are, as a rule, dark brown, with a lighter but sharply defined edge. Sometimes they are almost black and a little tuft of hair grows from their surface. These are piliary naevi. A few others present the characters of vascular naevi. They become anaemic on pressure, and resume their pink colour when the pressure is removed. On the back of the hands there is a large number of small petechial spots, but the patient informs me that they are not permanent; they come and go. On examining in detail the distribution of the cutaneous tumours we find that they are present in great quantity on the patient's scalp, more especially towards the occiput. I counted as many as twenty of the larger ones in that region alone; indeed there are more of the larger sized tumours over a given area on the scalp than over an area of similar dimensions on any other part of the patient's body. They are pre-

sent on the scalp in great variety : small, flat and sessile; shiny and whitish in colour, larger globular ones sessile or slightly pedunculated and of a bright pink colour, contrasting strongly with the white scalp; all kinds are seen. Some are tense, feeling like a grape; some again are less resistant, and others a mere skin, like the grape with its contents extruded. The consistency of the majority is uniform, but in a few of them a small hard nodule is felt in the interior. Leaving the scalp we find a few small sessile tumours on the forehead, with a larger one, about the size of a coffee-bean, above the left eyebrow; another of the same size a little behind the outer canthus of the left eye, and one immediately above the right eyebrows towards the root of the nose. There are several small ones over the right temporal region; these can be better felt than seen. Patient has two small warts, separated by a groove on the left ala of his nose. His auricles are free both from pigmentation and from tumour growths. There are several small tumours over his right supraclavicular triangle, mostly of the size of lentils. On the opposite side the

condition is much the same, except for the presence of the larger ones about the size of a small mistletoe berry. The anterior aspect of his thorax which is marked by a strong piliary development is covered with small tumours varying in size from a pin head to a coffee bean. The larger ones, however, are much fewer in number than the smaller ones. There is a lipoma over the middle third of his sternum; it is about a centimetre in diameter and is surrounded by several of the smaller cutaneous tumours. Posteriorly the tumours are even more plentiful, and as regards size they are much the same as anteriorly, except for a large one about the size of a coffee bean over the inferior angle of the right scapula, and another one internal to it about the size of an acorn; this one is seen to be growing from a large pigmented patch. There are also several comedones scattered over the posterior aspect of the thorax. Some of these are incorporated in the tumours. In front there are a few comedones in between, and associated with the tumours, but they are not so numerous as posteriorly. The patient's abdomen is covered with the smaller

sized tumours. From constantly lying in bed with his back propped up and his trunk flexed on his thighs the surface of his abdomen is thrown into a number of transverse folds. The skin in the grooves between these folds is red, moist and hot, and exhales an unpleasant odour. A few small tumours are seen in these grooves. By palpation, little lumps which can hardly be seen projecting on the surface are felt in the thickness of the skin. Posteriorly in the lumbar and sacral regions the skin is covered with small tumours of which only a few reach the size of a coffee bean. Some have no contents, and merely look like little tags of skin. Many of then cannot be made out except by palpation. Along the lateral aspects of his thorax on either side there are several tumours visible; but they are mostly of the smaller sizes.

In the upper extremity the tumours are not numerous. On the right side there is only one tumour in the upper arm; it lies on the outer surface of the limb in its upper third. On the forearm there are a few small sessile tumours with spread out bases. They are better evidenced by palpation than by inspec-

tion. There are some which cannot be seen at all; but are distinctly felt in the thickness of the skin in various parts of the limb. On the antero-external surface of the same forearm about two and a half inches below the bend of the elbow there are two linear cicatrices each 1¼ inches long, and practically continuous with each other along the line of the radius. They are the marks of the removal of two tumours for examination. At the lower extremity of the upper cicatrix a hard nodule is felt and is seemingly due to the development of the remains of a tumour which was not completely excised. In the upper half of the postero-internal surface of the same region there is another cicatrix running longitudinally. It is not so well marked as the other two and is also the site of an extirpated tumour. On the left side there is a couple of small tumours in the upper arm; there are two also on the forearm, rather small ones, about the size of lentils; they are situated on the radial aspect of the limb and long hairs are seen to be growing from both of them. There are no tumours below the wrists, either on the palm or on the dorsal aspects of the hands.

With regard to the distribution of tumours in the perineum, the two large growths on either side of the anus have already been described. There are none to be seen on the pubis or on the genitals.

In the lower extremity the tumours are not numerous; there are only a few to be seen here and there on the outer surface of the thigh, in the upper part. On the middle third of the anterior surface of the left thigh there is a short linear scar showing the spot from which a tumour was removed. Apart from this there are no growths visible from below the upper third of the thighs downwards; none on the feet, either on the soles, or on their dorsal aspects.
The PIGMENTED SPOTS as already indicated, are situated chiefly on the trunk. They occur in their greatest abundance on the sides of the chest and the abdomen, and on the hips. On the posterior aspects of the trunk they are not so numerous as anteriorly, but they are generally of a darker colour. There is a large irregularly rectangular pigmented patch slightly internal to the inferior angle of the right scapula; it is roughly about the size of a half crown piece

and it has a tumour the size of an acorn, and several comedones growing from its surface. Like the rest of the large patches it is somewhat obliquely directed. Lower down in the left lumbar regionthere is another large "coffee and milk" coloured patch and not so dark in shade as the one just described. It is somewhat lozenge shaped and is about 1¼ inches long and ¾ inches broad at its widest part. Its long axis is obliquely directed in a horizontal plane of the body. Still lower down on the sacrum there are four or five patches varying in dimensions froma threepenny piece to a sixpence; two on the right buttock and one on the left. A few smaller ones are seen on the hips and on the upper and outer surfaces of the thighs. The spots are scanty towards the middle of the thighs and they get less and less going down the limbs until there are hardly any near the feet. The soles are quite free from them.

In the Upper extremity the spots are present, though not at all plentifully, from the shoulder down to the wrist. There are a few on the dorsum of the hands, but none on the palms or between the fingers. They are absent on the face and neck.

The hairy naevi are comparatively few in number; they are irregularly distributed over the body and so are the vascular naevi. The best marked one of the latter is situated on the outer surface of the upper third of the right thigh. It is about the size of a threepenny piece. It grows pale on pressure and regains the bright pink colour when the pressure is taken off.

The conjunctival and buccal mucous membranes are free from pigmentation and tumour growths.

With the description of these pigmentary sopts and patches and of the cutaneous tumours, both those which project from the surface and those which are only slightly apparent to the eye, and lastly those that are not visible at all on the surface but whose presence is revealed in the thickness of the skin by palpation, we have not by any means exhausted the abnormalities which our patient Flond presents for examination. On careful palpation we find that there are still large numbers of other lumps to be felt over various parts of his body. These swellings unlike those we have previously studied are not in the

thickness of the skin, but manifestly below it. They form no part with the skin and are not displaced with it. They appear to lie between the skin and the subjacent cellular and aponeurotic tissue. To the touch they are smooth and not very hard. Their feel is somewhat like that of a testicle or an enlarged tubercular gland, say in a child's neck. In shape they are mostly oval, rounded, or irregular. They occur, as a rule, in chains, like the beads of a rosary and the cord which unites them can be distinctly felt very like a thickened radial artery at the wrist. They appear to follow the line of the subcutaneous nerve trunks and their branches. These swellings occur on some of the deep nerve trunks as well. They are freely mobile under the skin and are capable of lateral but not of vertical displacement from the line in which they run. By making the skin over them tense, their displacement can be seen as well as felt. When the force which displaces them ceases to be exerted, they quickly resume their usual position. They are not painful as a rule; but some of them when pressed upon give rise to lancinating

pains which shoot along the part. This is particularly observable in the limbs. Their principle sites are on the limbs and chiefly on the anterior and internal surfaces in the upper extremity and on the anterior, internal and posterior surfaces in the lower extremity. On the trunk they are found on the abdomen principally towards its lower part, and along the intercostal spaces. A few may be felt on the thorax in front and behind. In the lumbar and sacral regions they are not plentiful. There are none to be felt on the scalp or along the supra-trochlea or supra-orbital nerves; none on the face.

A chain of small moveable swellings is felt along both borders of the sterno-cleido-mastoid on either side of the neck, but as the feel of the tumours in other parts of the body is very like that of a set of enlarged lymphatic glands it is not possible to pronounce absolutely on the nature of the swellings just mentioned. They are capable of displacement from side to side but vertical movement cannot be satisfactorily made out. There are no enlargements felt in the descending sternal, Clavicular and Aer-

omial branches of the cervical plexus.

In the upper extremity chains of tumours are felt below the skin beginning from the axilla and downwards to the inner side of the upper arm and on the front of the forearm. In the latter region some can be identified with the radial nerve.

These tumours vary in size from a lentil to a small gooseberry. There are some in the axilla standing out prominently larger than the majority. About an inch below the bend of the elbow a tumour about the size of an acorn is felt beneath the skin which can be freely moved over it in every direction. There are none of these tumours on the hands or fingers. On the front of the chest there are a few, but of the smaller sizes. Laterally, however, along the intercostal spaces there are several large ones about as big as acorns to be felt. On the right side along the sixth intercostal space there is a large one about the size of an unshelled almond; it is freely moveable under the skin and causes no pain on pressure. On the abdomen they are mostly small varying from a lentil to a coffee bean in size. In the groin as in the

Axilla several nodules are felt both above and below Poupart's Ligament. They are displaceable from side to side, and vertically to a certain extent. It is, however, not possible to say whether they are enlarged lymphatic glands or tumours of another description. All along the front and inner sides of the upper part of the thighs chains of these small swellings ranging in size from a split pea to an acorn are felt beneath the skin. They run down the limb in every direction in an arborific manner. They give no pain when squeezed. There are not many of these swellings to be felt on the outer side of the thighs or below the middle of the limb anteriorly. Posteriorly in the upper part a few can be felt on deep palpation, though not very distinctly along the course of the great sciatic nerve, his wasted hamstrings making the nerve more available to the touch then normally. Lower down in the Popliteal space a long chain of subcutaneous swellings can be distinctly made out. When the great sciatic or the internal popliteal nerve is pressed upon the patient starts with a pain that shoots along the limb. He feels the same pain when he

tries to walk or to raise his limbs above the plane of the bed. The enlargements along the course of the popliteal nerves are not perceptibly of any greater size than the majority of those already described; their dimensions all vary within the same limits.

On the left leg, in the course of the external popliteal nerve three fingers breadth behind and below the head of the fibula a tumour the size of an acorn is felt and on the right leg there is also a somewhat smaller swelling to be felt symmetrical in position with the one on the left leg. A few may be felt on the upper part of the inner side of the front of the legs; below this there are none to be made out; none in the feet, none on the toes.

It is necessary to pass now to another set of phenomenon which the patient exhibits and which are not less interesting than those we have just described. Before doing so, however, we shall summarise the preceding observations as follows:-

1. Tumours raised from the surface of the skin.
2. Tumours felt in the thickness of the skin.
3. Pigmented spots.
4. Pigmented patches.
5. Piliary Naevi.
6. Vascular Naevi.
7. Tumours felt beneath the skin in connection with subcutaneous nerves and their branches.

Opposite Page 27.

Fig.V. Flond. To show the patient's usual expression.

Apart from these objective signs which are remarkable enough in their way we find it is impossible to look at Flond without being struck by his dull listless and apathetic appearance. He lies all day in one position on his back with a fixed vacant stare. His gaze is distant as if he were contemplating an object far beyond the walls of the ward. He never initiates a conversation with any one, nor does he take an interest in himself or in his surroundings. He never expresses a desire for anything and he even neglects the broth that he lives upon, for he takes no solid food, until it has grown quite cold and the attendant compels him to take it. He has a supply of tobacco but he rarely takes the trouble to smoke.

AfAfterhaving been engaged for several days in taking observations on his case, I told him that I would like to make him a small present and whether there was anything he fancied. But no, he had'nt the remotest idea. He didn't know and he didn't care.

On the first day I commenced my observations I was unaware of the fact that he was nearly deaf and I spoke to him for a long time in ordinary tones but

all the information I could get from him was "No, NO." and sometimes "Yes, Yes." for a change. He never took the trouble to tell me that my questions were inaudible and he evidently was not in the least bit curious to know what I was saying, which, considering I was an utter stranger in the ward, and of a different nationality to himself, was very remarkable, more especially for a Frenchman.

It is certainly possible to arouse his attention; but it is necessary to keep at him constantly. The moment he ceases to be engaged he relapses into his previous state of torpor. But this apathy seems to be only one of a number of psychical phenomena observable in the patient. On getting him to speak, it becomes evident that his intellect is below the average. He is but a poor scholar and is barely able to read a few short words. Mental arithmetic, except for the simplest calculations, is quite beyond him. He is at a loss to find words to express himself and his memory is a very poor one, both for recent and for remote events. On different occasions he gives conflicting answers to the same questions.

Opposite Page 29.

Fig.VI. Flond. Note feeble development and large pigmented patches.

He has no delusions or hallucinations so far as I have been able to make out, and he says that he sleeps pretty well at nights.

Taking a general survey of the patient, we remark his poorly developed, stunted, emaciated form. His head, which is covered with coarse, black hair, sprinkled with grey, appears too big and out of proportion to the size of his body. His cutaneous sensibility is greatly disordered.

On pricking him with a pin it is found that his scalp is anaesthetic all over, and likewise his auricles, both on their anterior and posterior surfaces. There is, however, no abolition of sensibility to pain over his forehead, eyelids, cheeks, nose or lips. Over the chin and on the neck there is complete anaesthesia. He is hyperaesthetic over the ribs on both sides, but the sensibility over the rest of his trunk is quite lost. In the upper extremity there is loss of sensibility to pain all over the right arm from the shoulders downwards. Posteriorly the anaesthesia ceases at the metacarpophalangeal joints of the hand and anteriorly at the wrist. The palm and

palmar aspects of the fingers are hyperaesthetic. The same hyperaesthesia exists in between the fingers. On the left side the axilla is hyperaesthetic. The outer surface of the upper arm and the inner surface at the level of the insertion of the pectoralis major are hyperaesthetic. In the rest of the limb the sensibility is lost down to the wrist anteriorly, and to the metacarpophalangeal joints posteriorly as on the right side. The palmar surface of the hand and the backs of the fingers are hyperaesthetic.

In the lower limbs the skin over both buttocks is hyperaesthetic, beyond this the thighs and legs down to the ankle joints are anaesthetic. The feet are hyperaesthetic both on their dorsal and plantar aspects. Deep pressure on the thighs posteriorly, more especially on the left thigh and over the calves elicit great pain. The same fact is not observable in the upper extremity. His sense of touch is not affected to any extent. His muscular sense is very uncertain, sometimes it appears to be pretty good and at other times it is hopelessly at fault. His sensibility to heat and cold is diminished all

over his body but it is not lost. He is subject to tingling sensations about his body, and feelings of numbness and cramps, more especially in his lower limbs. His eyes are blue and he has a well marked arcus senilis. His pupils are contracted, irregularly circular and unequal, the left being smaller than the right. They react to light and accomodation, but their movement is sluggish. His field of vision is markedly diminished. He is able to recognise ordinary Roman capitals at a distance of nearly two feet, but he us unable to read small type at any distance whatever.

He is completely deaf in the left ear, as a resudt of an Otitis following Scarlatina as before indicated. In the right ear the faculty of hearing is weak but not lost.

His sense of taste is dull; he takes a comparatively long time to tell the difference between sugar and salt. His sense of smell is not keen; it is with difficulty that he recognises essence of peppermint and he is unable to detect any odour in Camphor, though he readily tells Acetic Acid. His pharyngeal and laryngeal reflexes are preserved but sluggish. He

has never had any difficulty in keeping his water and he has full control over his sphincters. His palmar reflex is marked on the right side, but abolished on the left. The plantar reflexes are much exaggerated on both sides. The abdominal and crenasteric reflexes are preserved. His knee jerks are markedly increased on both sides; there is no ankle clonus. His wrist tendon reflexes are exaggerated on both sides but more so on the left.

His grasp is feeble in both hands, but comparatively more so with the right than with the left hand. On getting him to stand he is seized with tremors of his lower limbs.

The conditions of his other systems are breifly referred to as follows:-

Alimentary System. Teeth fiar, gums spongy looking. Tongue fairly clean. He has a very poor appetite and no desire at all for solid food. In fact he has not taken any solid food for the last two years on the plea that solids do not agree with his digestion, He lives on milk & broth. His bowels are usually confined and he needs to get some opening medicine from time to time. His sclerotic is a little muddy.

Haemopoietic System. He is somewhat anaemic. Spleen not enlarged. There are some nodules felt in his neck, his axilla and his groin. Nothing remarkable about his thyroid gland.

Circulatory System. Pulse 68 per minute, vessel wall thickened; slightly irregular in force and time; expansion fairly large; maximum slowly attained and not sustained; tension between the beats low. He gets dyspnoeic when he exerts himself, but not when he is lying quietly in bed. He has never fainted except at the time when he had Typhoid Fever. His heart sounds are very feeble but no bruits can be made out. There is no increase of the Cardiac dulness to be made out.

Respiratory System. He has a very emaciated chest flattened at the apices and bulging out towards the lower part. The resonance over his lungs is diminished at the apices and increased at the base, both anteriorly and posteriorly. The breath sounds are harsh at the apices but feeble at the bases. There is no disturbance of the respiratory ratio, and there are no accompaniments. He has no cough.

Integumentary System. Already fully described.

Urinary System. He micturates about five times in 24 hours, thrice during the day, as a rule, and twice at nights. The quantity at each act is small. His urine is high coloured, S.G. 1026 - Reaction - acid - Deposit of mucus and urates - no casts, There is no albumin or sugar or other abnormal constituents.

Reproductive System. His genital organs are fully developed. He is unmarried.

We have now before us the typical features of the disease known as Generalised Neurofibromatosis a name given to it by Dr. Pierre Marie and which is now pretty universally adopted in this country. These features are, as we have seen:-

1. Cutaneous pigmentation.
2. Cutaneous tumours.
3. Tumours of subcutaneous and other nerves.
4. Psychical and other nervous disturbances.

Viewing this remarkable combination of affections, we naturally ask ourselves are we dealing with an isolated case in which the symptoms have grouped themselves fortuitously; a chance case which has no greater right to be classed as a separate disease than one of Typhoid Fever or of Pneumonia which did

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Fig.VII. Guillaume. Note expression, tumors and spots.

not follow the classical course? Or, on the other hand have we to do with an affection in which the signs and symptoms are as constant as those of Typhoid Fever or Pneumonia are apt to be, in which the disease, if varying sometimes within certain limits, as all diseases do, from a too arbitrary type, yet exhibit certain features so constantly as to justify the recognition of its place in medical literature?

The question is best answered by the statement of another case.

I purposely select that of the other patient I saw along with Flond in 1895, because his death having taken place in the interval we shall have the opportunity later on of studying the results of his autopsy. The facts which follow here are taken from my own notes on the case, and from the clinical records which Dr. Marie very kindly placed at my disposal.

The patient - a male named Ernest Guillaume, aet 43, was admitted into the Hotel Dieu on December 11th 1894, and transferred to the Hospice de Bicêtre in November 1895. His occupation was that of an office-boy. His father died at the age of 91 years

as a result of a hemiplegia which had lasted for five years. His mother died from suffocation at 62, the patient could not say whether she had any tumours about her body. His father had none. He had no brothers or sisters. As a child he began to walk rather late, not, in fact, till he was five years of age. Up to the age of 10 he was always suffering from colds in the head and he had a constant cough. At 10 he was admitted into the Hôpital de l'Enfant Jesus for an eruption of "boils" on his face. He was discharged after a year, but, though cured of his boils, his cough was still troublesome. He got on fairly well up to the age of 21 though his cough never left him and he was more or less constantly subject to dull pains about his joints and his muscles. Sometimes these pains were worse than at other times; but all the same he was never driven to his bed. He did not perform his military service. He said that he had been overlooked; but nevertheless, he acknowledged that he was physically incapable of being a soldier even if the authorities had not neglected him. At 21 he had a severe attack of Gastric Catarrh

which confined him to bed for a month. After that he kept in prétty good health except for his cough, until he was 27 when he contracted a gonorrhoea which lasted for three weeks. At 30 he had another attack of Gastric Catarrh which, as on the previous occasion, laid him up for a month. After this he had no other serious illness until April 1894, when he was obliged to seek relief at the Hôpital de la Pitié from a Pleurisy which was later on followed by an effusion. His pleural cavity was aspirated and two litres of fluid removed. He remained for three months at the Pitié, and during this time he coughed continually and grew very thin. After his discharge he felt utterly unfit for work and he led a hand to mouth existence. He had no home and at night he usually slept under a bridge or in one of the municipal shelters. In the early part of November 1894 he had a copious haemoptysis and thereafter he frequently spat blood in small quantities. He had been a very hard drinker in his day. During his career as an office-boy from the age of 26 he used to drink three glasses of brandy in the mornings before taking any

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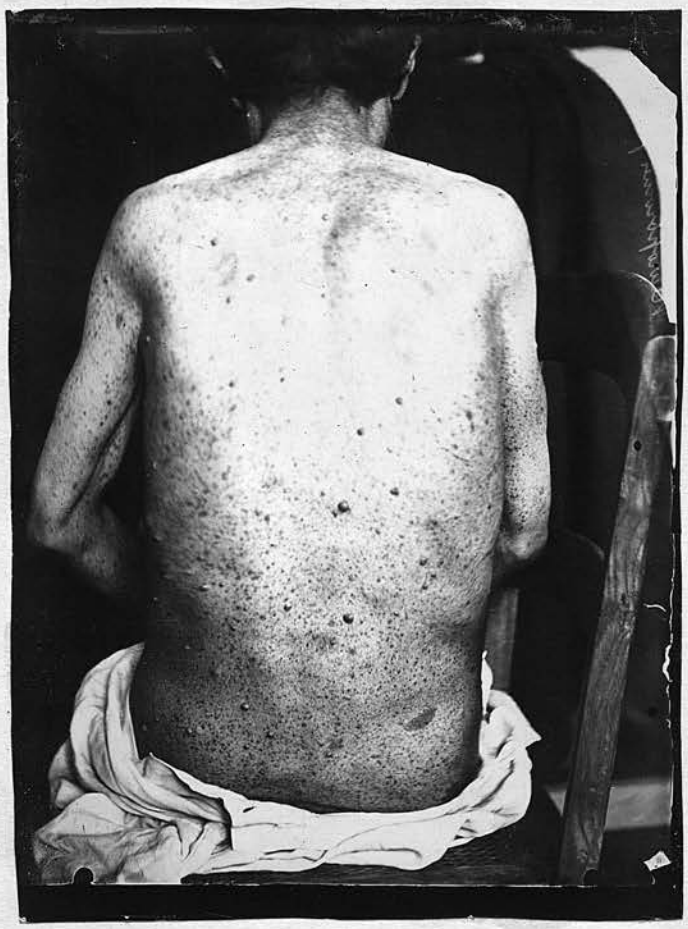

Fig.VIII. Guillaume. Note tumors and pigmented spots. The large pigmented patch above the right buttock is well seen; observe its oblique direction.

food. At midday he courted an appetite with two glasses of absinthe. With his breakfast (midday meal) he drank a glass of wine and after the meal, a cup of coffee with a small glass of brandy to wind up. Before dinner he repeated his two glasses of absinthe and he washed down the meal with a glass of wine. He faithfully carried out this régimè, except when circumstances rendered it impracticable from the age of 26 up to the time of his admission into the Hôtel-Dieu at 43.

On admission patient appeared to be at least 10 years older than he really was. Stunted, emaciated, feebly developed, he also bore a distinctly cachectic look which, undoubtedly, the Pulmonary Tuberculosis from which he suffered to some extent accounted for. He had a look of utter wretchedness. His muscles, especially those of his limbs were greatly wasted and in height he was only 1.535 metres.

On stripping the patient it was found that pigmentary spots and patches of various dimensions were scattered over his body, which was literally covered with tumours ranging in size from a millet seed to a walnut.

The colour of the pigmented spots varied from different shades of "coffee and milk" to a brownish red. In size they ranged from mere punctiform stains to a pin's head or two pins' heads put together. There was nothing remarkable about their shape, they were usually round or irregular.

The patches varied in size from a threepenny piece to a shilling and were sometimes larger. They were usually oval in shape or irregularly rectangular. In colour they resembled the spots, those on the trunk were either obliquely or transversely directed. Their borders were in all cases sharply defined from the surrounding skin. In a general way the spots were more numerous on the parts where the tumours occurred in their greatest numbers. A few piliary naevi were to be seen about his body and about a dozen small vascular naevi were also counted. The tumours were most numerous on the trunk and at the roots of the limbs, and presented a great variety of characters for examination. They were far more abundant than they appeared at first sight owing to the presence of many very small ones which did not at once catch the eye. The average size of the larger ones did not

exceed that of an ordinary grape; a single one on the left side of the Thorax reached the size of a walnut. The great majority, however, ranged in size from a millet seed to an acorn. Their shape varied greatly; a large number was just barely perceptible as minute hemispherical swellings on the skin; some could only be made out by palpation, whilst others appeared like small nipples projecting from the surface of the skin; they were mostly globular and sessile, but a few were slightly pedunculated. It was observed, however, that the pedunculation did not appear to be regulated by the size of the tumors, very small ones showing this character equally with the larger ones. The large tumor on the left side of the Thorax was absolutely sessile. The colour of the tumors was in many cases identical with that of the surrounding skin, but a great number and generally the larger ones were purplish, some were pinkish, and some again had "coffee and milk" coloured spots on their surfaces as if they had originated from the sites of the spots. Comedones appeared on the surface of a certain number of them. Some of the tumors

were smooth, others had their surface creased as if their contents had shrunken.

To the touch, the consistency of the growths was equally variable; some of them presented the false sense of fluctuation characteristic of lipomata and their feel greatly resembled that of a grape in which the stones have been removed. In others the feel was like that of a grape in which not only the stones but the pulp as well have been removed and nothing but a tough skin left. As in Flond's case all these tumors occurred in the skin, and were incorporated in its thickness. A good many could not be seen at all on the surface, their presence being only made out in the thickness of the skin by palpation. Many of this class, more especially the smaller ones felt as if they were situated on the undersurface of the skin, and not within its actual thickness. Like all the rest these were of course displaced with the skin of which they formed part.

The patient declared that for as long as he could remember he had these tumors and spots about his body, and that his mother used to tell him that he was "born like that". They were not painful, and

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Fig.IX. Guillaume. View of front and side of chest. Note the large multilobular growth on the left side.

never gave him any discomfort. The regional distribution of the tumors was as follows.-

On the scalp one or two only were made out; there were three on the forehead near the roots of the hairs and two small ones on the face but none on the Auricles. On the neck they were few in number in front but plentiful posteriorly; on both of these aspects they were mostly small. On the trunk the distribution was not uniform; in front there were none to be seen on the Sternum, but they were fairly numerous on the rest of the Thorax; they greatly increased in numbers towards the lower part of the abdomen and were very plentiful at the roots of the lower limbs. They were plentiful also on the flanks; the largest one on the body was situated towards the centre of the line drawn from the hollow of the left axilla to the great trochanter on the same side. It was 35 millimetres in its long axis, and 18 millimetres at its narrowest part. This tumor was peculiar in the fact that it was multilobed and seemed to be formed by the coalescence of a large number of smaller tumors. There were several of those multilobular tumors to been seen on various parts of the

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Fig.X. Guillaume. View of left side and back.

patient's body, but none of them reached anything like a size approaching that of the one just described. On the posterior aspect of the trunk the tumors were very plentiful; laterally they were not confluent, but towards the middle line of the back they ran together in great numbers. As was observed, in front they became more numerous as the roots of the limbs were approached. There were a few at the root of the penis, but none on that organ itself or on the scrotum.

In regard to the limbs, the tumors were, generally speaking, more abundant at the junctions of the former with the trunk than towards the periphery.

On the right shoulder there were some small ones, and about four or five of the larger ones and several small ones over the whole length of the arm. There were two on the dorsum of the hand, but the palm was absolutely free.

On the left shoulder they were pretty numerous and some of them fairly large, but on the arm there were only four or five small ones and none on the hand. In the lower extremity they were particul-

Opposite Page 44.

Fig.XI. Guillaume. View of skin over patient's abdomen showing tumors, spots and patches.

arly numerous at the root of the thighs; on the right side they occurred in great numbers on the anterior aspect of the upper part of the thigh, and grew less plentiful going down the limb. There were three small ones present on the dorsum of the foot, but except for these none existed from below the knee downwards. On the left thigh they were also more numerous in the upper part, but less so than on the right side and going down the limb they rapidly decreased in numbers. Posteriorly, only three were present on the limb. Below the knee there was only one, and this was situated on the outer side of the dorsum of the foot. On the left buttocks they were pretty numerous and of fair size, but there were not many on the right.

On the limbs and on the anterior aspect of the trunk the tumors were mostly of the same colour as the neighbouring skin or they were less pigmented than those situated on the posterior surface of the trunk the latter being as a rule purplish or pink like the vascular naevi.

Turning to the distribution of the spots and patches, it was found that these were scarce on the

face. There were none present on the auricles, but on the neck they were very plentiful and almost confluent, especially at the back. The spots were fewer in number on the thorax than on the neck; their numbers became more considerable going down towards the abdomen and were especially so on the flanks and over the pubic region where they presented a darker tint than higher up the body. The genitals were quite free from them. It was also observed that apart from the effect caused by the pigmented spots and patches the colour of the skin on the sides of the chest and abdomen was of a darker tint than that of the rest of the body. There was a large patch, about three centimetres long and one centimetre broad, below the margin of the false ribs on the right side; it it was covered with fine downy hairs, but the skin in its immediate neighbourhood was also similarly covered. The pigment which was so abundant on the neck and abdomen was conspicuously wanting over the sternum. On the posterior aspect of the trunk the pigmented spots were very wide spread. In regard to the extremities the spots were most abundant near the roots of the limbs and their numbers greatly decreased towards the periphery; this was observed both in the

upper and lower limbs. The hands were almost completely free from pigmentation and only a few small spots could be made out here and there on their dorsal surface. A similar condition was noticeable on the feet. The pigmented patches were very plentiful. The largest one was situated on the outer side of the right thigh in its upper part; it was 45 millimetres in its longest diameter, and 26 millimetres in its broadest part; it was obliquely directed. On the right half of the front of the thorax there were three patches, each being as large as a sixpence; there was another one of about the same size below the false ribs. There were none on the left half of the thorax; posteriorly there were four to be seen. On the right arm there were two, of which one was situated over the head of the humerus; on the left arm there were three. In the lower extremity there were two on the right thigh one of which has already been described and one on the calf, On the left side there were three or four on the thigh. Besides these pigmented patches several piliary naevi were observed; their longest diameter varied from 35 millimetres to 15 millimetres. Long coarse hairs grew

from their surface and some of them were in a slight degree raised from the surrounding surface. On the outer surface of the left arm at about the level of the insertion of the Deltoid there was a very dark brown, almost black, one with long hairs growing from it and a little below it there was a large patch covered with downy hairs. The vascular naevi were chiefly localised on the abdomen; they were mostly small and varied from a pin's head to 5 or 6 millimetres in diameter. There were four or five over the right hypochondrium and one in the supra pubic region a little to the left of the middle line. The buccal and conjunctival mucus membranes were completely free from pigmentation and from the presence of tumours. There was no indication of any system or symmetry in the distribution of the tumours and spots; they seemed to be scattered about at hazard. On the trunk the larger spots were generally speaking transversely or obliquely directed. In the lumbar region, on the right side, there were two tumours about as large as pigeons' eggs felt in the thickness of the skin; they were very soft and gave the impression of being lipo-

mata, they were not raised above the surface of the surrounding skin. A few more of these lipoma-like swellings were observed, one on the left side of the back of the thorax, one on the same side in the lumbar region, and one on the outer surface of the right upper arm.

Although carefully looked for there were no swellings made out in connection with the subcutaneous nerve trunks in any part of the body and likewise no thickening of nerve cords were to be felt. On the outer surface of the left arm, a little above the insertion of the Deltoid, there was a tumour of the appearance and consistency of a subcutaneous lipoma. In this case therefore the principal objective features which the skin presented were:-

Pigmentary Spots.
Pigmentary Patches.
Cutaneous tumours.
And a few (?) lipomata.

But here again the psychical and other nervous phenomena which were so remarkable in Flond's case are by no means wanting. Guillaume's wretched, utterly depressed, cachectic appearance has already been indicated. He lay in his bed for several months

without ever quitting it, or expressing a desire to do so. He took no interest in anything and never spoke to any one unless he was first addressed. The only effort he ever made at the Hôtel-Dieu was to write a letter to Dr. Marie asking to be transferred to the Bicêtre Hospital. His memory was very poor and his intelligence much below the average. About three months after admission it was observed that he stammered and had great difficulty in finding words to exptess himself. He confessed that he had once been confined in a lunatic asylum and that he used to take "giddy turns" during which he usually lost consciousness and fell to the ground. His tongue revealed the scars of old bites which he said had been inflicted during his fits. He did not know whether he used to utter any cry before the "giddy turns" came on and he had never heard any one at the asylum say that he was epileptic. His cutaneous sensibility was in the greatest disorder; there was diminished sensibility to pain on both sides of the body but especially on the left side including the face. Sensibility to touch was greatly diminished, more especially on the

left side. His sensibility to heat and cold also showed the same abnormality. His sight was weak and his field of vision markedly contracted. His hearing was dull, and so also were his senses of taste and smell. He had no sexual appetite.

When made to get out of bed for purposes of observation, it was found that he could walk a little, but his movements were slow and devoid of energy. The muscular power of his limbs was very feeble; his grasp was weak and nerveless. He complained of pains in his head and all over the rest of his body in the joints as well as in the muscles. He was tender on pressure all over his vertebral column but there were two particularly painful spots, one over the cervical region and the other over the lumbar region. The pains about his body were more or less constant but they were not particularly localised in any region, although, if anything, they were more severe about the articulations, especially in those of the elbows. He was greatly subject to cramps in his calves and in his thighs, especially in the mornings. During his stay in hospital all these pains,

except those in the head, rather diminished in intensity than otherwise. His tongue on being protruded was tremulous and deviated in a marked manner to the left side, but there was no hemiplegia, or even any muscular paresis. His pharyngeal reflex was preserved. For some time before his admission into the hospital he had noticed that his micturition was accompanied with great straining. Sometimes he took about five minutes to begin to make his water. Later on he found that he required to micturate almost every hour and notwithstanding this frequency the quantity passed on each occasion was very considerable. From December 29th 1894 to January 7th 1895, he passed 3-4 litres daily.

From	7th	to 11th	January - 4	litres	daily.
"	11th	to 22nd	January - 4-5	"	"
On	22nd	& 23rd	January - 5½	"	"
"	24th	& 25th	January - 4	"	"
"	26th	& 27th	January - 4	"	"
"	28th		January - 4	"	"

The urine was of low specific gravity and contained no sugar. He had full command over his anal sphincters. His knee-jerks were exaggerated on both sides.

In addition to all these disorders Guillaume

was the subject of a Pulmonary tuberculosis of which the signs were very evident. His chest was emaciated and the supraclavicular hollows were well marked, especially on the right side. Percussion was attended with considerable pain on that side and the patient could not lie on it. On auscultation pleuritic friction was heard at first over the right base without any signs indicating the presence of fluid, but later on an effusion took place and on a few occasions aegophony was distinctly made out. On percussion the note at the apex was dull and the breathing distinctly bronchial. On the left side mucus râles and a few consonating crepitations were heard over the base. The patient's fingers were markedly clubbed his nails presenting the parrot's beak rather than the watch glass deformity.

Such then is Guillaume's case, which, as we have seen, bears a close analogy to that of Flond. In both cases we have the same cutaneous lesions, the pigmentary spots and patches, the vascular and piliary naevi and the cutaneous tumours with all their various characters; in both cases also, we have the same feeble muscularity, the stunted development, the weak

intelligence, the pronounced mental depression, the cramps, the asthralgic pains, the various disorders of sensibility, the affection of the organic senses, and other nervous manifestations. It must be remarked that no swellings were made out on the course of the subcutaneous nerves in Guillaume's case, but when we come to deal with the evidence furnished by his autopsy we will find that there was good reason pathologically as well as clinically for regarding the two cases as being instances of the same disease. In fact, we have no lack of examples of analogous combinations of signs and symptoms, and later on we shall quote several cases of the same nature published by competent observers of whom Professor von Recklinghausen must always stand foremost.

Comparing anew the two cases, we must note the difference in the mode of appearance of the tumours and pigmentary spots. In Flond's case the patient tells that up to the age of 52 he had no spots or tumours about his body and that the spots were preceded by the tumours which made their appearance in crops, first on his scalp, and subsequently on the rest of his body. Guillaume on the other hand affir-

med in the most positive manner that his mother had told him that he was "born like that", namely, with the spots and tumours. In regard to the distribution of the tumours we find that while in Flond's case they were relatively greater in respect to size and numbers on the scalp than on other parts of the body, in Guillaume's case the roots of the limbs were the seats of the greatest numbers and the cephatic extremity hardly at all affected.

It being granted that, on the strength of the facts already submitted, we have made out a satisfactory case in favour of regarding the combination of symptoms grouped together under the name of Generalized Neurofibromatosis, as a separate disease, we naturally confront ourselves with the questions"What is the aetiology of the disease?" Do we know anything of the Morbid Anatomy? How is the disease diagnosed? What are the variations in its Clinical features? What is its usual course and termination?"

All these are questions which we shall carefully consider in their proper places.

AETIOLOGY. Looking back to our two cases, we note that the disease, in so far as the spots and tumours were concerned, in the one first shewed itself late in life, while in the other, according to the patient's statement, it was congenital. This variation in the mode of appearance in the cutaneous lesions of generalised neurofibromatosis is a matter of not infrequent occurrence, but, nevertheless, in the great majority of cases the lesions are congenital or at any rate they date from early infancy which practically comes to the same thing, because it is not usually required that a disease should necessarily manifest itself actually at the time of birth to be congenital. Freidreich's Disease(Hereditary Ataxia) may be quoted in support of this statement as a notable example of a disease commonly regarded as being congenital but in which the symptoms are not as a rule apparent before about the age of 8 years.

In considering the congenital evidence of the presence of generalised neurofibromatosis we must bear in mind the view that the cutaneous signs are not always so complete as in the case of Guillaume who was born with tumours and pigmentary spots on

his body or as in a case of Brissand quoted by Feindel[1] in which the patient C.H. had the pigmentary spots on his body ever since he could remember, and said that the cutaneous tumours were certainly present in great numbers and as large as peas when he was barely 10 years of age.

The pigmentary spots may be and commonly are the only signs at birth, as in the case recorded by Vincenzo Brigidi[2] where a man aet 64 was born with pigmentary spots on his back and later on during his infancy small cutaneous tumours appeared on his left arm; this condition remained stationary until at the age of 54 when other small tumours began to grow in various parts of his body, and in the course of ten years had increased to several hundreds. In another case quoted by Feindel[3] the patient, a woman, R.B. aet 42, in whom the symptoms of generalised neurofibromatosis were well marked, stated that ever since she was an infant she had "coffee and Milk" spots about her body and that she had been told they were

1. E.Feindel. These de Paris, 1896. P.63.
2. Vincenzo Brigidi. Multiple Neurome der peripherischen Haut und Muskel nerven mit Fibroma Molluscum. Monatshafte f. prakt Dermatol. No.5 1894. p.191.
3. Feindel. Loc. cit. p.60.

"mothers' marks". In her case the tumours also appeared in crops, the first coming on at the age of 17. In other instances of this disease, the tumours alone may be congenital as in the two cases observed by Atkinson[1] where a brother and a sister aet 56 and 50 respectively had tumours on their body from early infancy. In a case of the same nature observed by von Recklinghausen[2] the patient, a woman N.K, aet 55, said that the tumours were noticed on her body ever since she was three years of age.

In another case observed by the same author, the patient, a male M.B., aet 49, said that the tumours existed on his body for as long as he could remember.

Modrzejewski[3] records a case of the same malady in a woman J.M., aet 37, whose body was covered with tumours from her earliest infancy, and lastly we may quote the case Dr. J.F.Payne[4] where the patient, a

1. J.E.Atkinson (Baltimore) Two cases of Fibroma Molluscum. New Yord Med.Jour. Dec.1875. p.601.
2. F.von Recklinghausen. Ueber die multiplen Fibrome der Haut und ihre Beziehung zu den multiplen neuromen. Berlin, 1882. (Hirschwald).
3. Modrzejewski. Gaz.Lebdom. de Med. et de Chir. Paris 1881. p.508.
4. J.F.Payne. Trans. Path. Soc. Lond, 1887 Vol.38 p.69.

woman G.M., aet 37, who was undoubtedly suffering from generalised neurofibromatosis stated that the tumours had existed all her life as far as she could remember. In certain cases, the sole congenital sign is a single tumour, usually a large one, called by Bondet[1] a "major" tumour, the other evidences of the disease coming on later in life. Cimmino[2] has recorded an instance of the kind where the patient, a man aet 42, suffering from generalised neurofibromatosis was born with a "major" tumour over the sacrum and the left buttock, the smaller growths making their appearance during infancy.

In cases where there is no evidence of the congenital appearance of any of the signs of the disease, though Feindel asserts that generalised neurofibromatosis is always congenital, the first cutaneous lesions may appear at any age from say 10 or 12 to 50 or more, and in these instances the multiple tumours may simultaneously appear in large numbers all over the body or they may appear in small crops with a longer

1. Bondet. These de Paris. 1882.
2. Cimmino. Su di un caso di fibrome multipli cutanei, con metamorphosi sarcomatosa. Giornale Italiano delle malattie venerce e della pelle. Mars 1891.

or shorter interval between each successive crop; sometimes each interval extends over a period of several years. Lahmann[1] published a case (Case 1 of this author's observations on generalised neurofibromatosis) of a man, aet 54, in whom the cutaneous tumours first appeared about the age of 12, and continued to increase in numbers up to the age of 20. In Joseph Grindon's[2] case where the tumours were very numerous and absolutely typical of the disease, their appearance was not made until the age of 20; while in another case, observed by Payne[3] they appeared at the age of 49. In a case published by Lionel Beale and quoted by von Recklinghausen the first sign of the disease in the patient aet 60 was the appearance at the age of 23 of small cutaneous tumours all over his body.

It not infrequently happens that a "major" tumour appears at a more or less advanced period of life and the smaller multiple tumours develop sub-

1. Lahmann. Die Multiplen Fibrome in ihrer Beziehung zu den Neurofibromen. Virch.Archiv. t.101.
2. Joseph Grindon. St.Louis Medical Fortnightly 1892.
3. Payne. A case of Molluscum Fibrosum combined with tumours on the nerves. Clin.Soc.Trans. Lond. Vol.22, p.189.

sequently. This seems to have been the case with the patient Flond, who told me that he had been inconvenienced by a big lump - "major" tumour, - near his anus for some time prior to the appearance of the tumours on his scalp. This "lump" is well shown in the accompanying photograph which I took for the express purpose of demonstrating it. In Flond's case also the tumours seem to have come on in crops though the interval between each crop was of brief duration. In a case of Lebest quoted by von Recklinghausen, an old man, aet 70, was observed to have a large tumour on his right thigh. A few months later this tumour was found to have greatly increased in size, and innumerable small tumours at the same time made their appearance on his body.

We may therefore summarise the mode of appearance of the cutaneous lesions as follows:-

I. Congenital. II Non-Congenital.

Congenital includes where the disease first manifests itself in infancy as well as at the time of birth. Under this heading we have the cases where:-

(a) Both spots and tumours appear at birth or soon after.

(b) Spots alone appear.

(c) Tumours alone appear.

(d) A single "major" tumour appears.

Under Class II, we have the cases where -

(a) Cutaneous lesions appear simulataneously all over the body.

(b) Cutaneous lesions appear in crops with long or short intervals between each successive crop.

(c) More or less late appearance of a "major" tumour with subsequent development of other lesions.

In veiw of the fact that the majority of cases of generalised neurofibromatosis are congenital Marie[1] regards it as possible that the occurrence of noncongenital cases is even rarer than is generally supposed, owing to the frequency with which the pigmented spots must escape observation in early life. Feindel[2] as we have indicated, goes further, and asserts as a fact that every case of generalised neurofibromatosis is congenital. His principal reasons for this statement are that in a child born with a predisposition to a certain disease, if the latter manifests itself during early infancy all the world is agreed that the disease is congenital; further that in these cases of generalised neurofibromatosis where the patient

1. Marie (Pierre) Leçons de Clinique Medicale 1894. p. 261.
2. Feindel. loc.cit. p.17.

tells that the tumours were present on his body as long as he can remember, we have no means of knowing whether they were strictly congenital, and for all practical purposes we may regard them as such, and further still that in the cases where the disease appears late in life, we may take it that the congenital predisposition was merely late in manifesting itself. He also quotes in support of the late manifestation of a congenital predisposition a case of Brissaud[1] where a supernumerary finger appeared in an individual aet 32. It is evident that Feindel hopelessly confuses the meaning of the term congenital, with heredity, diathesis, and predisposition, and even though his assertion may be correct, the grounds upon which he bases it are altogether insufficient. In a case exhibited by M.M.Marie and Albert Bernard[2] beforethe Société Médicale des Hopitaux and published in the Society's Journal there appeared to be no doubt whatever that the first signs of the disease consisting in cutaneous tumours and pigmentation appeared at the age of 27.

1. Brissaud. Communication a la Soc.Anat. Paris 1876.
2. Pierre Marie et Albert Bernard. Bull. et Mem. Soc. Med. des Hop. Paris, Feb. 27, 1896.

If as Feindel[1] states that all the world is agreed that a disease appearing in earliest infancy is congenital, we can hardly grant him that the same concert exists in regard to diseases manifesting themselves for the first time at the age of 27. And if not, a fortiori, we can scarcely regard, on the grounds advanced by him, such cases as that of Payne[2] in which the disease began at the age of 49, and that of Flond which commenced at an even later period in life, as being congenital.

Dr. Marie[3] states in his Clinical Lessons that in certain carefully observed cases it seems that the appearance of the disease gives absolutely no suggestion of its being congenital, and elsewhere he states that this noncongenital mode of appearance seems well established. He throws out the suggestion that these may be acquired cases or instances of the late appearance of the disease in a congenitally perverted organism. This last idea which is a good one but which, as Dr. Marie has acknowledged to me, is purely specu-

1. Feindel. loc.cit. p.13.
2. Payne. Clin.Soc.Trans. Lond. V.22, p.189.
3. Marie. loc.cit. p.261, and Bull. Soc.Med. des Hop. Fev. 27, 1896, p.202.

lative; is practically what Feindel rashly assumes to be a definite fact.

Undoubtedly, owing to the fact of the disease having in the majority of cases been determined to be of congenital origin, it is not unlikely, as Marie suggests, that the cases in which congenitality has not been made out are instances of imperfect observation, for we must bear in mind that in a matter of this kind positive evidence is of far greater value than negative information. Lack of the power of observation among the laity is well known to the medical profession and of this there can be no grosser instance than a case which occurred in my own experience when a companion of mine in Trinidad, a youth of 20, confided to me that he had recently lost a testicle. He stated that he had been attempting to take a bare back ride on a donkey grazing in a certain park and that the animal showed its displeasure by kicking him below the belt. From that moment according to his graphic narration, one testicle disappeared in his belly and he had never seen it since. To my uninitiated mind the story appeared at the time, if peculiar,

yet plausible enough, but later on, when I came to Edinburgh I had not filled many terms at the University before I diagnosed the case without any difficulty whatever, as one of undescended testicle. But here was the case of an intelligent young man who had lived for twenty years without observing until his attention was drawn to the fact by an accident, any irregularity in the symmetry of an apparatus which, unfortunately, perhaps, excites the curiosity of the average youth more than any other part of his surface anatomy. Hence, returning to our generalised neurofibromatosis, while it is not likely that parents are apt to see non-existent tumours or coloured spots about the bodies of their babes, or that later on the children are likely to so err, it does not at all follow that these signs are necessarily absent if unobserved. And so it comes to pass, that whilst we are unable in view of the insufficiency of the proofs adduced to give Feindel's bold assertion our unqualified support, yet we do not altogether regard with disfavour the theory of the possibility or even the probability of the congenital origin of all cases of generalised neurofibromatosis. The question of congenitality

naturally raises that of heredity. We ask ourselves, - "If the majority of these cases are congenital, nay, if in every case of Generalised Neurofibromatosis, however tardy the appearance of the disease, we may presume the existence of some developmental perversion of the tissues, may not the individuals so afflicted hand down the same vice to their progeny? May not the disease, in short, be hereditary as well as congenital?"

Well, in a few cases though not as frequently as may be expected the hereditary element is made out. Landouski[1] quotes two cases of this kind, where in one a father and in the other a mother exhibited symptoms of generalised neurofibromatosis, identical with those which subsequently appeared in their children. We may perhaps arrange these cases under the headings of those which are directly hereditary, as in the instances quoted by Landouski, and those in which the heredity is collateral. Among the former we may refer to the classical case of the Geng family, reported by Czerny and Hecker and quoted in almost every work that has appeared on the subject, in which Rosina

1. Landouski. These de Paris 1894. p.17

Opposite Page 67.

Fig.XII. Susy Merschel. Case of congenital plexiform neurofibroma of elephantiasis type, after Herczel.

the mother and her daughter Theresa both suffered from well marked symptoms of generalised neurofibromatosis. It was stated on medical evidence that Rosina maternal grandfather and granduncle suffered from the same disease. The former had numerous tumours on his body, some of which reached the size of an ordinary fist, and the latter had a large tumour on his back. Rosina's brother also had several tumours about his body, and in Theresa referred to above there was no doubt whatever about the presence of the disease; she had a growth of enormous volume in her lumbar region, numerous small cutaneous tumours over her body and several subcutaneous swellings, some being as large as hen's eggs on the peripheral nerves. Another analogous case is that published by Herczel[1] in which Susy Merschel, the daughter of a woman suffering, from generalised neurofibromatosis, exhibited unmistakeable symptoms of the same disease. She presented a congenital growth on the external aspect of the left elbow and fore arm; this condition resembled a sort of elephantiasis. In the occipital region there was another tumour of fair size. Both of these lesions

1. Herczel. Ueber Fibrome und Sarcome der peripheren nerven. Ziegler's Beitrage zur Pathol. Anat 1890. t.viii. p.38.

Opposite Page 68.

Fig.XIII. Mrs Merschel. Case of generalised neurofibromatosis - after Herczel - Patient is the mother of Susy Merschel whose photo is given on preceding page.

belong to a class of tumours of which we have not yet spoken, namely, plexiform neurofibromata, which, as we shall show later on, are merely other forms of expression of the same condition, generalised neurofibromatosis. In addition to the tumours mentioned Susy had bead like swellings in the region of both brachial plexuses; similar swellings were also felt beneath the thickness of the skin, along the line of the cutaneous nerves of both extremeties; in addition to this, the left arm on which the elephantiasis-like growth was situated was diffusely pigmented all along its surface, from the fingers up to the axilla, and further there were pigmented spots and patches all over the rest of the body. Her mother's case was very interesting. Herczel who had Susy under his care, insisted one day on examining Mrs. Merschel, who had denied that there was any other case of tumour growth in the family. On being stripped it was found that she was covered not only on the trunk, but on the extremeties as well with fibromatous nodules varying in size from a pin's head to an ordinary fist. Her cutaneous sensibility was diminished on the trunk to such an extent that she was able to permit the ex-

cision of several of the tumours without being anaesthetised. Her entire body was covered with pigmented spots and patches, this condition being especially well marked on the abdomen and on the extensor aspect of the upper extremeties. In places where the pigmentation was diffused, brown spots varying in size from a pin's head to a lentil were seen superadded on the already pigmented surface. These spots were irregular in contour and not symmetrically disposed, they were closely aggregated together, but nevertheless each individual spot was quite distinct from its neighbour. Above the umbilicus a little to the right of the middle line there was a large oblong patch deeply pigmented and its dimensions 3 centimetres by 4. Another patch of about the same size was situated on the upper third of the front of the right fore arm. There were three or four sessile fibromatous nodules on the scalp. In the lumbar region two vascular naevi were observed. The skin of the neck was the seat of a deep diffuse pigmentation and two hard fibrous nodules were felt in the right half of the thyroid body. It was remarked that her daughter Susy also had similar nodules in the thyroid body. There

were no tumours or any thickening of the subcutaneous nerves. Besides Susy, Mrs. Merschel had two other children aged six months and ten years respectively, but they showed no signs of generalised neurofibromatosis. Apart from the startling revelations made from Mrs. Merschel's examination, Herczel also succeeded in eliciting that the former's father (Susy's grandfather) had likewise suffered from birth from similar tumours; he lived to an advanced age and had died ten years before the observations on Mrs. Merschel were made. It was not possible to trace the disease further back in the direct line.

Ochterhong[1] records a case in which a negro woman and her child suffered from the disease, and Hilton Fagge[2] quotes an instance recorded by Virchow in which the father, grandfather, and brother of a patient afflicted with generalised neurofibromatosis had all suffered from multiple fibromata of the skin.

Launois and Variot[3] quote an instance recorded by Nicaisse in which the latter observed several indiv-

1. Ochterhong. American Archiv. of Dermatol.1875.July.
2. Fagge and Pye-Smith. Principles and Practice of Medicine, 3rd Edit. Vol.II. p.925.
3. Launois et Variot. Etude sur les nevromes multiples Rev.de Chir. juin, 1885.

iduals of the same family to be affected with multiple neurofibromata. Von Recklinghausen[1] also calls attention to the influence of heredity in causing the appearance of neurofibromata in several individuals in the same family. Hitchcock[2] many years ago records an instance in which there were three cases of multiple neurofibromata in the same family, the mother Elizabeth Clark, aet 81, had several hundreds of the tumours about her body. Her daughter also named Elizabeth had them too, and had been operated upon for the removal of one as large as a hen's egg, at the age of 10. Samuel Clark, aet 46, the son of the elder Elizabeth began to have tumours on his body at the age of 24; in his case tumours were also made out beneath the skin along the lines of the subcutaneous nerves.

The collateral cases are those in which two or more individuals of the same family are afflicted with the disease, though their parents were free from it. The case of the Lyons family recorded by Atkinson of Baltimore and already referred to may be cited as an instance. Here a brother and a sister, Timothy and Ellen Lyons presented multiple neurofibromata on

1. von Recklinghausen. loc.cit. p.62.
2. Hitchcock. Am. Jour.Med.Sci. 1862. Vol.43. p.320.

their bodies from infancy; there is however a suspicion of direct heredity in this instance, the patients having said that their father had some kind of tumour or other about his body. In von Recklinghausen's observations the case of Marie Kuntz is quoted in which the latter and her brother presented the symptoms of generalised neurofibromatosis. In the case of Marie, the disease began with the appearance of tumours at the age of three. There was no history of the parents being affected. Such, then, are a few examples of the collateral cases which are mostly congenital. It is, however, when we come to deal with the cases which appear late in life that we encounter the greatest difficulty in trying to determine a hereditary influence, whether direct or collateral. It is quite possible for an individual in whom the disease appears late in life, even if he is able to assert that neither his father suffered from the same disease to have an aunt or an uncle in whom certain of the lesions were present but not observed, thereby rendering unavailable the evidence of collateral heredity. We may go even further and suggest that

even the absence of any visible signs of the disease on the parents or grandparents would not necessarily exclude the question of heredity for if according to Marie's suggestion there is a developmental perversion of the tissues, which as Feindel asserts is present in all cases and merely requires an exciting cause or a stimulus of some kind to bring out the disease, the tardy cases would represent those in which the proper stimulus was not encountered till late in life. and pushing the theory to its logical sequence, we can conceive the cases of individuals having in their organism the potentiality of a neurofibromatosis but who managed throughout the course of their lives to escape altogether the exciting cause necessary to determine the disease; these individuals though never having themselves presented any signs of neurofibromatosis could nevertheless transmit the potentiality to their children, and the latter if less fortunate than their parents would sooner or later be assailed by a stimulus sufficient for the development of the disease in the aetiology of which, of course, no hereditary element would be apparent. The theory upon which the preceding arguments are based, is not without

a certain amount of fascination and Feindel is completely lured away by it; but the whole fabric depends on the assumption of a congenital malformation of the tissues and this is exactly what Feindel does without any substantial proof.

But whatever may be the real facts there is no dearth of other causes to which the disease is attributed by different observers. Von Recklinghausen[1] whose beautiful monograph on the subject of generalised neurofibromatosis is indispensable to all those who take an interest in the disease, discusses at length the possibility of the latter being of the nature of an infection in which the nerve trunks are specially implicated and he indicates its resemblance in certain features such as tumor formation, pigmentation, anaesthesias etc. to Leprosy. n Brigidi[2] also called attention to the fact that in 1883 Bockhardt having moculated the micro-organsim of erysipelas into a cutaneous fibroma, the latter subsequently assumed a

1. Von Recklinghausen. loc. cit. pp.66-76.
2. Brigidi (Vincenzo) loc. cit. p.244.

condition resembling a elephantiasis; on these grounds he asked whether the neurofibromata were not also due to an infection. Among a number of writers Gernet[1] replied in the affirmative and so did Burow[2], but Philippson[3] after a careful research more especially with the use of Gram's method failed to find any micro-organisms in the neurofibromata. According to some authors the toxins of certain of the infectious fevers are the causes of the disease, and certainly a generalised neurofibromatosis has been observed to follow in the wake of Typhoid Fever, Scarlatina, Diphtheria, Rheumatic Fever, and Measles; but still the disease has been known to follow other forms of poisoning as well, notably in a case recorded by Helra and Pick and quoted by Marie[4] and von Recklinghausen in which, in a man aet 58, neurofibromata had appeared at the age of 10, after recofering from arsenical poisoning. If therefore the toxins of the fever appear in certain cases to determine the disease, their influence cannot be regarded as being of a specific nature.

1. Gernet. Virch.Archiv. T.41.
2. Burow. Virch.Archiv. T.38.
3. Philippson. Beitrage zur Lehre vom Fibroma Molluscum, Vurchow's Archiv. T.110.
4. Marie. loc.cit. p.263.

According to Landouski[1] hereditary degeneration bad hygienic conditions and cold are all factors determining the appearance of the disease.

Of these we may recall to mind that our patient Flond attributes all his ill to the frostbitisg which he suffered. Landouski theorises on the possibility of the subjects of the disease being degenerates, and the lesions they present being merely the stigmata of their condition. Lausent[2] a pupil of Variot's quotes two cases of the disease which he observed in the Central Hospital for Prisoners. These two cases should support Landouski's idea for the patients being delinquents, are, according to Lombroso, necessarily degenerates, but Landouski very probably did not hear of these two cases or if he did he failed to realise the great support they lent to his theory, for he goes on to admit that as a matter of fact the stigmata of degeneration, whether physical or mental, and, I should add, or both, are manifested from birth while as we know in many cases the disease has certainly not showed itself until late in life.

1. Landouski. loc.cit. p.18.
2. Lausent (Em.) N evrome Multiple "France Med" 1889.

Hebra[1], however, writes that all sufferers from this disease present a common type which appears peculiar to them, and elsewhere he states that all the subjects of molluscum who had come under his observation were stunted in bodily growth and of more or less limited mental capacity. The two cases under our own observation certainly bear out this statement in its entirety. Von Recklinghausen[2] also draws attention to the intellectual deficiency and even a condition of cretinism characterising certain, but, he says, only in the minority of instances, and the manifestations are not such as to give rise to the conclusion that the brain or the spinal cord plays any part in the production of the lesion affecting the peripheral nerves. And Landouski himself, after briefly discussing the question of hereditary degeneration, comes to the conclusion that if that factor is to be considered at all it can only be in the light of a predisposing, rather than of a direct, cause. This idea of a cause predisposing an individual to the acquirement of the disease, is, as we must observe,

1. Hebra. K.U.Gesellsch. der Aerzte in Wien 1864. Nov.4th.
2. Von Recklinghausen. loc. cit. p.66.

entirely at variance with Feindel's assertion of a congenital malformation of the tissues in all cases, for on this supposition unless the degenerates had in their organism the particular malformation proper to the disease, they would run no risk of acquiring it. But the list of causes would not be complete without the inclusion of traumatism and indeed we find it strongly advocated by some as being responsible for the production of a generalised or a localised neurofibromatosis. A remarkable case is quoted by Laurent[1] In 1881 a man, then being 20 years of age, received a blow on his right side. Two or three months afterwards he noticed that a small tumour had grown on the spot where he had been struck. Four years later he had the growth operated on by M. Pean, who diagnosed it as a lipoma. Soon afterwards some other small tumours appeared simultaneously in almost every part of his body, but chiefly on his limbs. On examining the patient it was found that characteristic pigmentary spots were on his body and he dated their appearance from 1881. Xavier Delore records a similar case occurring in his experience.[1]

1. Laurent Em. Nevromes multiples France Med. 1889. July 6th? p.905.
2. Xavier Delore. Neurofibromatose cutanee avec Xanthome profonde du bras droit. Gaz.des Hop 1896. Avril 28.

Even von Recklinghausen supports the idea of traumatism being the cause of neurofibromatosis and very naturally so for does it not fit beautifully into his theory of an infection? Given a blow to devitalize the part; given a wound to break the solution in its continuity, the way is open to the entrance of the specific organisms and the rest is merely a question of the result of the battle with the phogocytes! Next it has been noticed that the distribution of the pigmentary patches bears sometimes a close similarity to that of the lesions in certain forms of Herpes, the origin of which is attributed by Brissaud[1] to a localised infection of a single segment of the spinal cord. These lesions which include various forms of eruptions & bands of hyperaesthesia appear to be restricted in the affected region to a line drawn round the body in the same horizontal plane throughout. The pigmentary patches in generalised neurofibromatosis are not continuous in their distribution over the trunk, but it is said that their situation and direction are often such that a line join-

1. Brissaud. I. Le zona du tronc et sa lopographic.
II. La metamerie spinale et la distribution peripherique du zona. Bull.Med.Paris, Nos. 3 & 8.
III. Sur la distribution metamerique du zona des membres. Presse Medicale, Paris 1896, No.4.

ing them all would describe the circumference of the body in a single plane; this is supposed to give the idea that the resemblance in the distribution of the lesions in the two diseases may arise from a similarity of origin, namely, an infection of the spinal cord. But the fact of the case is that the pigmented patches though they are sometimes horizontally directed and occur in multiples on the same horizontal plane of the body, do not invariably show this tendency; indeed they are as a rule very irregular in their distribution. On the other hand Herpes, though frequently not of spinal origin, always tends to assume a circular distribution. We think the comparison made between the two diseases rather far fetched, and it certainly lends no support to the theory of its infectious origin of generalised neurofibromatosis.

The last group of causes, which we shall merely mention, is another advanced by von Recklinghausen[1] namely friction, and mechanical irritation; these he states if they do not actually cause the development of neurofibromata at any rate exercise a certain amount of influence in that direction.

1. Von Recklinghausen, loc.cit. pp. 63 & 64.

Well now, what does all this diversity of opinion in regard to the causation of generalised neurofibromatosis show? Obviously that the question is still unsettled and that although most of the factors advanced as causes may be directly or indirectly connected with the production of the disease, yet none of them can be looked upon as specific. It certainly has been established that in the majority of cases the disease is congenital and from time to time also a hereditary influence is made out; and these circumstances would seem to favour the suggestion of a developmental malformation of the tissues concerned, but, after all, it is only a suggestion, and we have not sufficient grounds in the present state of our knowledge on the subject to accept it as a fact as Feindel has done.

Reasoning by analogy with what is observed in certain other diseases, most of the other factors mentioned may act as exciting causes in persons predisposed to the disease, or in whom the disease is latent, but in the first place we need to assume that certain individuals may be predisposed to neurofibromatosis or may have in them the potentiality of the

disease, and in the next place, we cannot in medical science always attach much importance to the result of analogous reasoning. We are not sufficiently well conversant with the rules which regulate the more subtle processes of the human organism, and things do not always turn out to be what according to our imperfect methods of reasoning we should expect.

In considering the possibilities of this complex question of aetiology in generalised neurofibromatosis the hint given to us by the discovery of nodules in the thyroid body of the two Merschels, must not be lost, and in view of the remarkable morbid conditions which, within recent years it has been discovered, that disease of this organ produced, we may ask ourselves whether generalised neurofibromatosis is not a hitherto unrecognised mode of expression of some morbid condition of the thyroid glands. The question is all the more worthy of consideration that recently Langhans[1] has drawn attention to a whole series of remarkable changes in the peripheral nerve trunks consequent upon excision of the thyroid gland.

1. Marie. Loc. cit. p.264.

And even if after careful observation the thyroid gland is found to have no connection with the disease, work done in that direction will always be of special, perhaps classical, value, in that it may represent the first attempts at proceeding on the right track in the search for the aetology of the disease; for apart from all possible causes aduced, when we carefully ponder over in our mind the general distribution of the lesions, those cutaneous tumors, those pseudo neuromata occurring in the viscera as well as on the skin and subcutaneous tissues; when we think also of those pigment spots and patches, and how invariably a certain number of the latter assume a particular shape and direction, and lastly of that peculiar cachexia and the various nervous and other phenomena, we feel we can hardly be dealing with a disease dependent on a vice or affection of any particular system, but rather one in which the whole organism is involved and we are somehow irresistibly driven to speculate on the possibility of generalised neurofibromatosis being of the nature of one of those glandular diseases such as is met with in the thyroid

gland or in the supra-renal body. I have refrained as much as possible from venturing into more or less risky hypotheses throughout the entire course of this work, but I am bound to say that I do not at all consider it unreasonable to suppose that this condition of generalised neurofibromatosis is produced by the absence, or deficiency, or malformation, or disease whatsoever of some gland, or secretory or excretory organ in the body, of whose presence, or of whose nature and function we are at present unacquainted. If this supposition were to prove true, we could at once understand how the disease is congenital sometimes, and how at other times it appears at varying periods of life according as this glandular body or organ is congenitally malformed, or wanting, or affected in some way or other; or causing as it becomes diseased later on.

It is true the Anatomists or to the anatomo-pathologists that we are to look for light upon this ha hazy subject, and one can only express a fervent hope that in every case of generalised neurofibromatosis where the opportunity for performing an autopsy arises, the observations may be made in the most searching and exhaustive manner.

Opposite Page 83.

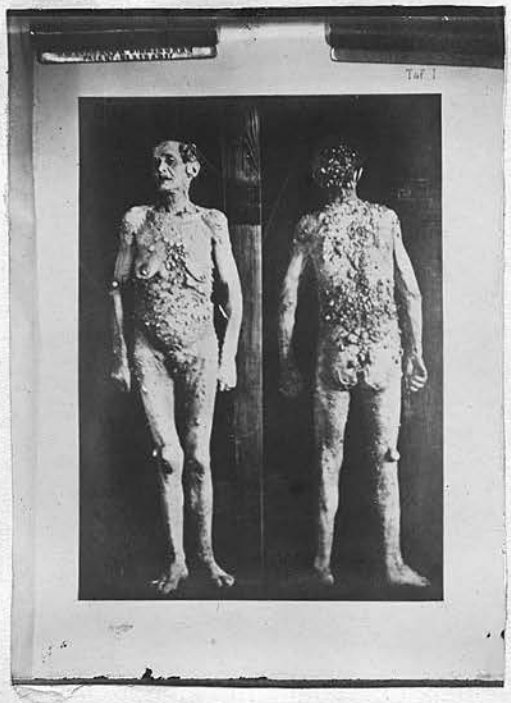


Fig.XIV. Case of generalised neuro-fibromatosis after von Recklinghausen.

We now pass to the consideration of the PATHOLOGICAL ANATOMY of generalised neurofibromatosis, under certain of its aspects, and in doing so, we cannot more fitly introduce the subject than by quoting *in extenso* the report of the P.M. Examination made in a well established case of the disease by Prof. von Recklinghausen, who was the first to work out the pathology of this disease in a really serious manner, and to whose investigations the greater part of our knowledge of the subject is due. The present observations were made on the body of Marie Kuntz, whose case we have already had occasion to refer to and the report is taken from von Recklinghausen's monograph already cited in several places.

"Marie Kuntz, aet 55, was admitted into Hos-
'pital in January 23rd 1879 for a haemoptysis from
'which she died a few hours afterwards. She was cov-
'ered with cutaneous tumours and told the nurse she
'had had them since the age of three and never suff-
'ered any inconvenience from them. Her youngest
'brother affirmed that she had been twice married and
'had given birth to 11 children, all of whom were de-
"livered with surgical assistance. They all died.

Opposite Page 84.

Fig.XV. Another case of von Recklinghausen's.

" This brother had on the back of his neck a soft subcutaneous mobile tumour slightly adherent to the skin, this tumour had three lobules on its inferior border and was harder than a lipoma. Over the last dorsal vertebra there was a tumour as large as a cherry stone; it was hemispherical, rounded, soft, easily mobile towards its deep part as well as towards the tegument which covered it. No tumours were found along the nerves.

P.M. Examination of Marie Kuntz's Body.

Very numerous tumours on almost the whole surface of the body; the majority pedunculated, the rest sessile; as a rule they are spherical; the largest ones are 4 or 5 centimetres in thickness. The tumours are covered by a somewhat smooth unbroken skin. Two of them, one over the sacrum and the other on the left side of the trunk are slightly ulcerated. Some of the tumours present on their top sometimes a depression and at other times a black point from which sebaceous matter can be expressed. The tumours are exceedingly numerous on the skin of the abdomen and of the chest; on the back they are

Opposite Page 84a.

Fig.XVI. Case of generalised neuro-fibromatosis.

confluent and of considerable size. There are numerous tumours on the back of the neck. All the tumours which have been described send prolongations into the subcutaneous cellular tissue. They have in part their principal seat in this subcutaneous tissue. They raise up the skin which is very thin over their sites. But side by side with the tumours just mentioned there are some which are simply subcutaneous and are not felt except by palpation. We shall refer to them later on. To the touch these tumours are of unequal consistency. On section it is seen that they are composed of a white soft and nearly diaphanous tissue which is also frequently opalescent. They seem to be formed of cords folded upon themselves. At the periphery they exhibit lobuliform prolongations which sometimes only exist only one side. The tumours both large and small permit of being completely reduced to mere flabby sacs with creases on their surfaces. Sometimes this effected with difficulty at other times easily. There are some small tumours (milliary and sub milliary) which have no relation with the subcutaneous cellular tissue and belong exclusively to the skin. There are numerous pigmentary spots on

"the skin and on the tumours, the left crural nerve presents at the origin of the saphenous a fusiform tumour (32 millimetres by 7 millimetres). The nerve grooves its posterior aspect. Above the left knee on the saphenous nerve there is another small tumour around the muscular branches of the crural nerve. There are two tumours on the lateral cutaneous nerve (femoro-cutaneous) of the leg limb, one being on the superior branch below the point of bifurcation, and the other a hand's breadth above. There are numerous tumours in the muscular branches of the left obturator nerve.

The following are the lesions observed in the right lower extremity:-

The muscular branches of the perineal nerve are considerably thickened especially the superficial one. Properly speaking, these are only thickened there are no fusiform nodosities along their dourse. The femoro-cutaneous presents no nodules above and below its point of division. The crural nerve at the level of the bifurcation of the deep femoral presents a nodosity of 26 millimetres in length situated on a branch which passes through the internal

"part of the thigh. The saphenous nerve presents during its course in the thigh four nodosities of which the largest is in the region of the knee joint. Below the knee there is another tumour on the saphenous nerve. There is nothing on the toes except a neuroma as large as a cherry on the middle toe of the right foot. Of the fourth left metacarpal there is a tumour the relation of which with the nerves cannot be made out, moreover it is very adherent to the skin.

On the right side of the trunk the posterior branches of the first and second intercostal nerve and the branches which pass to the hollow of the axilla present several nodosities. The third intercostal presents one on its course between the intercostal muscles. On the left side in the region of the 8th intercostal there is a nodosity at the point where the superficial branch emerges through the serratous magnus. A few branches of the brachial plexus also present small swellings on the internal surface of the axilla. The olfactory, optic, oculo motor, facial, and auditory nerves are free down to their smallest brances, from nodosities, and so also are the mental nerves. But the frontal and supra-

"orbital nerves possess several nodosities. There are none on the auriculo-temporalis. When the dissection of the cutaneous nerves was carried out further after the hints given by the growths found on the other nerves, numerous other very small fusiform swellings were brought to light on many of the nerve branches of the subcutaneous connective tissue. Search was made to find out if the subcutaneous tumours had any visible naked eye relations with the nerves; search was unsuccessful for fibromata of the back, but quite successful for those of the skin of the leg and thigh.

The first sacral nerve had several nodules at distance of 5 centimetres along its course. The second and third sacral nerves of the right side were smaller and affected with a diffuse inflammation; on the left side they presented some isolated nodules; these swellings reached as far as the sacral canal but not up to the dura mater. The pneumogastrics presented in the region of the neck a few small fusiform asymetrical swellings. Nothing in particular was noticed in the brain and spinal cord. The sympathetic branches of the neck and of the lungs have

"nothing wrong with them, but in the lumbar region a somewhat doubtful nodule is made out. The superior mesenteric plexus corresponding to the upper part of the jejunum presents some quite distinct neuromata; the same thing is noticed in the gastric plexus which presents some small isolated nodules. On the anterior surface of the left tibia towards its middle there are two transparent tumours situated side by side on the periosteum. The larger one is 11 millimetres in diameters, and the smaller one 6 millimetres, they are 4 millimetres thick and are of a pale red colour. A third tumour is situated below the middle of the tibia. On the right tibia there is a large tumour 7 millimetres thick and there are also three small nodules situated likewise on the periosteum and adherent to the bone.

In the region of the jejunum there is a well marked injection and chylification of the mucus membrane; there are two nodosities on the outer surface they are of firm consistency and coloured by a very vascular serous membrane; one of these two nodosities is of the size of a pea, and is divided into two tuberosities; the other is as large as a cherry stone.

"Towards the commencement of the jejunum there is an adhesion between the latter and the curved limb of an S shaped flexure in the small intestine. There is a second adhesion on the left surface of the mesentery and a series of radiating cicatrices start from it and pass on to the inferior surface of the transverse meso-colon. At the seat of this second adhesion, the wall of the jejunum presents a fairly large tumour which bulges freely into the abdominal cavity; it is composed of two parts of which the greater is of the size of a large walnut and is very much discoloured with black and red blood. The smaller one feels pretty hard in the midst of its mobile surroundings; it gives to the touch the sensation of a lymphatic gland. This tumour has a pedicle which takes root in the intestinal wall and sends a prolongation into the lumen of the intestine. After opening into the jejunum, a great number of nodosities were observed a little bigger than pins' heads and chiefly situated in the mucus membrane but nevertheless encroaching upon the submucus tissue. At one point there is a small ulcer. Towards the ileum, the gegunum presents some more ulcers with ragged edges and corresponding

"in position to Peyer's patches. The centre of the nodosities is not caseous. The ileum presents small ulcerations of Peyer's patches; the base of these ulcers is uniform and no granulations are seen at the periphery. These ulcers become of greater size lower down the bowel. The Cacum and the ascending colon present here and there a few follicular ulcerations. The transverse colon presents milliary nodosities on its external surface. They are yellow and probably fatty. The Rectum is loaded with a soft, slightly argilaceous mass; its mucus membrane is intact; there is, however, one sub-mucus nodule to be found with a cavity divided into two portions and containing some blackish matter. Numerous nodules are observed on the surface of the stomach; they are pretty scarce in the posterior surface, but as many as 20 are present on the anterior surface. In size they are milliary; they are also transparent and devoid of caseous matter in their centre; they are not arranged on the vessels but are distributed at hazard. The mucus membrane of the stomach is pale and unaltered, but a little rugose towards the Pylorus. The pancreas is normal in size. Above the opening

Opposite Page 91.

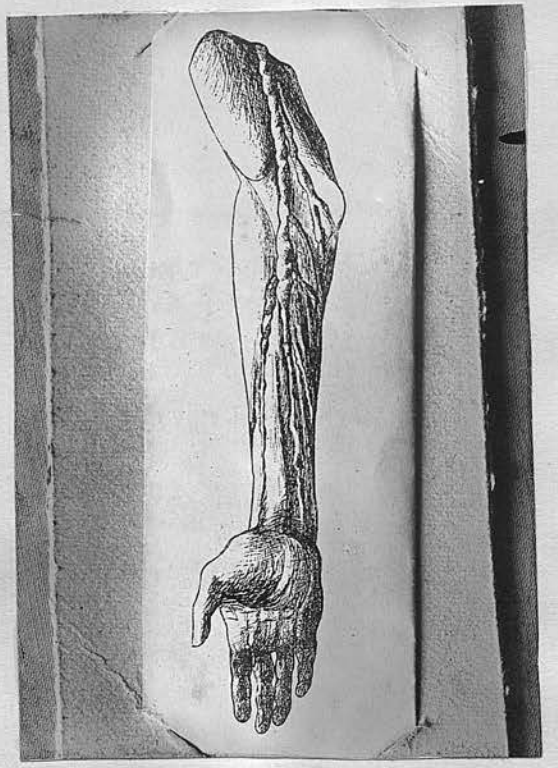


Fig. XVII. Right superior extremity described so as to show neurofibromata upon the subcutaneous nerves. After Robert Smith.

of the bile duct there is a bulge which corresponds to the portion of the pancreas which is in contact with the duodenum; at this part the duodenum is lobulated. and its mucus membrane fringed. The left kidney is of the normal size; its surface is sprinkled with pale whitish spots in the midst of which small transparent milliary nodules are seen here and there. On the cylinders of the medullary substance some small white nodosities are seen, but these are scarce, and are all without any central fatty nucleus.

The right kidney does not present a similar condition. On the posterior wall of the trachea there are numerous milliary nodosities surrounded by a red zone. A somewhat firmer nodosity, mobile, and smaller than a pea, projects from the right wall. There are tubercular cavities in the lungs. Death due to haemorrhage into the lungs. (aneurism of the pulmonary artery).

The observations may be summarised up as follows:-

Soft multiple fibromata of the external tegument of the subcutaneous cellular tissue. Neurofibromata of the cutaneous nerves, of the trunks and branches

Opposite Page 92.

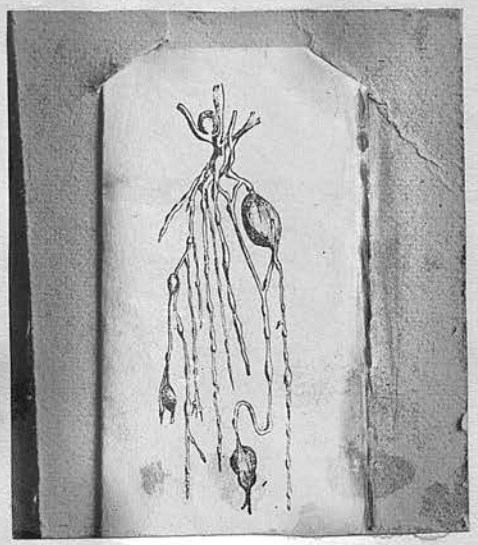


Fig.XVIII. Nerves of right superior extremity completely dissected out and showing neurofibromata. Note "major" tumors. After Robert Smith.

"of the nerves of the extremities, more especially of the lower extremity. Neurofibromata also of the sacral plexus, the vagus, the abdominal sympathetic nerves, the frontal branches of the trigeminal and of certain branches of the obturator nerves. Soft fibroma of the periosteum of the tibia. Milliary fibromata in the walls of the stomach and of the jejunum with two sarcomata as well, in the latter.

Old scaly indurations and cavities of the lungs. Tuberculosis of the kidney, perihepatitis, pericarditis, tuberculo-follicular ulcerations of the intestines. Death from haemorrhage into the lungs proceeding from the rupture of an aneurism of the pulmonary artery.

Here now is s summary of the results obtained after careful researches made in strict accordance with modern methods (by the use of Ormic Acid, Chloride of Gold, Picrocarmine and Haematoxyline) on the sections débris and bits removed from the tumors.

Tumors situated on the nerves.

The nerve fibres passing through the fibrous growths are perfectly normal; (no fatty degeneration

" or dissociaton). Sometimes they are a bit thin but they never lose their myelim; they can be easily followed throughout the whole length of their course in the tumor. From this aspect these tumors are altogether similar to those whichII(von Recklinghausen) examined in the case of Wartzbourg observed by Generisch. The connective tissue which forms the tumor, to speak correctly, is very finely fibrillar with long wavy bundles; the cellular element predominates in the connective tissue and the cells are flat and elongated. In this particular case the cells are all the more numerous when they growth is soft. The tissue of the tumors contains a network of vessels of large calibre. In all the neuromata the neoplastic mass is situated between the nerve bundles on the one hand and its lanullar sheath on the other, and moreover, the tumor substance may be isolated, not always without difficulty, from the intrafascicular connective tissue (endoneurium of Key and Retzins) though the latter is thickened. The outer limits of the tumors are very sharply defined. The epineurium is thickened and adherent when the tumor is

"situated on the bifurcation of a nerve trunk. In the case of the small cutaneous neuromata the structure is exactly the same and when the nerve plexus of the preparation was looked at more closely microscopic fusiform fibromatous nodules were observed in the the nerve fibres. It was in this case that the neurofibroma was transparent and rich in connective tissue cells, a circumstance which associates it with fibromata of the skin and establishes the transition.

Cutaneous fibromata.

In the cutaneous fibromata the tissue is harder than in the case of the preceding tumors, but softer than that of the skin. The cells are not vd very numerous, but they are more so than in the(normal) skin. The tissue immediately surrounding the tumor is harder, and gradually emerges into the normal tissue so that it can no longer be differentiated. At the parts where it is in contact with the normal tissue, it is fibrillated and nearly stratified. The substance of the tumor is not very vascular; the blood supply is derived from capillaries. I have said that each tumor is composed of rafters and the tissue uniting them is looser and contains elastic fibres.

"If the lobulated prolongations of which I have spoken are examined, it is seen that they contain sudoriparous glands; among others I have succeeded in discovering the entry of a nerve.

On the scalp hair follicles are found imprisoned in the tumour. The sebaceous glands are very numerous; they are seen lodged in depressions in the reticular layer and on shelling them out it is observed that they form the lower extremity of a thin process which goes up through the skin and is continuous with a tumour on the surface of the latter; this extremity is frequently crushed and flattened out. Sometimes these thin processes can be teased out on the slide; they then assume the shape of a horse-shoe and in such cases, the diagnosis lies between a neuroma which is curved in itself or which is more often the case a sweat duct binding together several small dissociated and altered glands. Although not frequently, it is possible to demonstrate in the growth a nerve trunk having five or six primitive fibres for its axis cylinder. The hair follicle is often altered and swollen as if the neoplastic tissue had pen-

"trated into it; sometimes it is obliterated. The muscles of the hair follicles are impregnated with the fibrous growth; their fibres are spread out from one another by the new growth. Their arteries are constricted and compressed and lose their integrity in this tissue; the adventia, however, remains and can be identified by its elastic fibres. In the sudoriparous glands only the epithelium remains; its connective tissue is replaced by the newly formed tissue. The same thing frequently happens in the case of the sheaths of the nerves which are found in the fibromata of the skin. Furthermore there is sometimes found at a considerable distance from the nerve loose connective tissue which may be taken for the remains of the lamellar sheath. The different microscopic views have permitted me to follow accurately the phases in the alteration of the sudoriparous glands under the influence of the morbid tissue growth.

1. In the first place a separation and uncoiling of the glomeruli.

2. The interstitial connective tissue becomes clearer and the fibres looser.

3. Formation of hyaline cylinders in a tumour of the duct; in this phase the periglandular tissue separates itself again from the tumour tissue perhaps on account of its elastic fibres.

" 4. In the last phase this separation is lost and the bends of the gland disappear more and more.

The uncoiling of the gland is admirably proved by the fact that I was able to isolate a horse-shoe branch in which the duct of the gland without taking into the account the blind ends was 9 millimetres long.

The epithelium of the sudoriparous glands was flattened out; sometimes it presents cystic swellings containing hyaline substance. The sweat ducts are situated towards the periphery of the tumour; it would appear as if the tumour tissue had grown between them, and I also think that they were not included in the tumour until at a late period of the latter's growth. I have not been able to make out that the tumours could have taken their origin from around the arteries.

Stomach and Intestines.

The nodules in the stomach and intestines were fibromata and not tubercles; (from their sites in the muscular coat, their size, etc.). The jejunum is not a seat of election of tubercle and moreover the microscopic examination left no doubt whatever of the fact. The delicate point was to find their relations to the nerves, a difficult matter because the nerves

"of the stomach have no hyaline substance. In any case, here is what I found in the substance of two fibromatous nodules in the intestine:-

Voluminous polygonal bodies with soft prolongations; these bodies were massed together and consisted of a granular substance with a few droplets of fat; they were certainly cells, but not of neuformation, nor yet were they giant cells, and as they occurred in the muscular coat of the intestine, I consider them to be the atrophied ganglionic cells of the myogastric plexus. Two large tumours of the jejunum were sarcomata, for they contained fusiform cells, with oval nuclei and frequently with granular protoplasm. In some localities the intercellular substance had disappeared to give place to cavities which were full of blood. I think, moreover that these were fibromata, that they had undergone sarcomatous degeneration.

Trachea

The milliary nodules of the trachea were tubercles.

Periosteum.

The tumor of the tibia was a pure fibroma with

"extremely soft tissue and very numerous cells. I found in them quite distinctly some small nerve trunks each containing five or six pale fibres presenting a double contour; these fibres had no laminar sheath and were situated immediately within the area of fibromatous tissue. In conclusion, the tumours of the periosteum are all together analogous to the neurofibromata."

I trust I may be pardoned for this lengthy quotation, but the observations were so carefully made, and the report so excellently drawn that I considered that it would not have been doing justice to the author or to the subject to have abbreviated it in any way, and moreover, such a model cannot fail to serve as a useful guide to any ordinary practitioner undertaking the autopsy of a similar case.

In addition to what we have already seen, it may be added that from the sum of the numerous observations which von Recklinghausen had the opportunity of making in reference to this disease he expressed his opinion that the cutaneous tumours termed mollusca fibrosa, or fibromata mollusca, or cutaneous fibromata

etc., are really neurofibromata or new growths of fibrous tissue developed in the deep layers of the skin or in the subcutaneous tissue around the small ramifications of the cutaneous nerves. He has, as we have seen, been able to make out the entrance of the nerve into the growth and in some instances its exit as well. The nerve fibres suffer a displacement or a teasing out, as it were, by the fibrous growth, but they preserve their integrity at any rate in the early stage in the newformation. Later on they are crushed by the fibrous growth and undergo an atrophy which finally causes their complete disappearance in many instances. Von Recklinghausen also states that he frequently noticed a growth having its origin in the subcutaneous tissue traverse the entire thickness of the cutis to form a tumour on the surface of the skin and this seemed to him as a proof that the new formation had followed the course of a cylindrical organ, such as a nerve, which itself t traversed the cutis. He observes also that though the proliferation of fibrous tissue begins in the first place in the connective tissue sheaths of the nerves the growth includes at a later stage of its development

the surrounding ducts and glands which being more resistant persist in the tumour even after the original nerve from around which the growth started has been crushed out.

We must call attention to the fact mentioned in the P.M. Report as we shall need to refer to it later on that von Recklinghausen expressly states he could not make out that the cutaneous tumours could have taken their origin from around the arteries.

As to the tumours found on the subcutaneous and deeper nerves there is no real difference between them and the cutaneous fibromata; their origin is from the connective tissue sheaths of the nerve trunks whose smaller ramifications are concerned in the formation of the cutaneous tumours. The nerve fibres do not undergo any change; there is no proliferation of nerve tissue and on these grounds Max Jordan[1] insists, very properly too, that they should not be called neuromata, for according to the rules laid down by Virchow[2] in order to constitute a neuroma there must be new formation of nervous tissue. As

1. Max Jordan. Pathologisch-Anatomische Beitrage zur Elephantiasis congenita. Ziegler's Beitrage 1890. T.VIII. p.71.
2. The International Encyclopaedia of Surgery Vol.3 pp. 600-1

a matter of fact, instead of there being any newly formed nervous tissue present, the calibre of the nerve cylinders rather tends to be thinned, a sort of atrophy in short, which though not so frequent in the fibromata of the nerve trunks as in those of the skin yet in a good many cases, causes the complete disappearance of the nerve fibres. These tumours therefore are not true neuromata but neurofibromata or false. Neuromata, as I prefer to call them, for the reason that while preserving the old name under which they have always been known the attention is at the same time drawn to their real nature. As we are on the question of Terminology, it is perhaps the opportune moment to mention the fact that while all observers are agreed to the origin of the pseudo neuromata, the same concert does not exist in reference to the origin of the cutaneous tumours, indeed the latter is a question that has given rise to more controversy among those who have investigated the matter than perhaps any other point in the pathological anatomy of generalised neurofibromatosis. And since, as I shall show later on, the question is still unsettled, I have adopted the term dermato-fibroma

which seems to me the most judicious thing to do, seeing that it describes the growth without committing one to anything in the manner that the other names, Neurofibroma, Molluscum fibrorum, Fibroma molluscum, Molluscum simplex, etc., do. And here also it is as well to call attention to the appropriateness of the name neurofibromatose généralisée, which Dr. Pierre Marie has given to the disease, a designation now pretty universally adopted in this country though it has not as yet to any extent found its way in British Medical literature. My translation of Généralisée as "generalised" is not an offhand anglicising of the French word. Norman Walker uses it in his admirable translation of Unna's work on the Histopathology of diseases of the skin and I have also seen the term vaccine généralisée rendered as "Generalised vaccine eruption" in a review of Dobson Poole's work on vaccine eruptions in the British Medical Journal.

Neurofibromatose is correctly translated "Neurofibromatosis" and not neurofibromata as I have sometimes seen it, the disease in these cases being called "Generalised neurofibromata" which is altogether

incorrect.

By adopting the name generalised neurofibromatosis we include all the growths having a nervous connection in whatever part of th body they may happen to occur and in regard to the skin tumours in particular if they are all neurofibromata as von Recklinghausen would make out, the name includes them, while if only part of them are of that mature, the others are covered by the term dermato-fibromata.

Altogether, therefore, I think the terminology employed, I am now speaking more especially with reference to the title under which I am writing this Thesis, though cumbersome from the length of the words, is nevertheless appropriate and excusable on this ground.

Returning to the pathological anatomy of the disease, as the cranial nerves in von Recklinghausen's case, quoted above, were not to any extent affected, I give here the result of the autopsy on a case published by M.Hausmann, and reviewed in the Bull.Soc.Med. Berlin, July 1895, as an interesting and instructive supplement to von Recklinghausen's case.

"Since Recklinghausen's work, nothing new has been published on this subject (fibromata and multiple neuromata,(sic)) because the latter seems exhausted. Recklinghausen drew attention to the relation between fibromata of the skin and fibromata situated on the ramifications of the nerves; the latter are fusiform tumours of a pretty firm consistency and sometimes of a milky appearance, (fibromata) or at other times soft and transparent (fibro-myxomata) The nerve fibres which traverse the tumours are pretty intact. This condition can be seen in the preparations which M.Hausmann has made in the case of a workman, aet 39, who had cutaneous fibromata since the age of 16. His body was covered with fibromata of the volume of a lentil; one only reached the size of a five frank piece; it was flattened out and situated to the left of the right nipple. P.M. few nerves were found unaffected, among the latter being the olfactory, the auditory, the optic and the facial, but the trigeminal, the pneumo-gastric and all the other cranial nerves were diseased and exhibited small tumours in the manner of a pearl necklace. The seats of the neuromata (sic) were all on the ex-

tra-cranial branches of the nerves mentioned. During life the patient had not presented any functional disturbances beyond the mechanical interference with deglutination caused by the tumours on the pneumo-gastric.

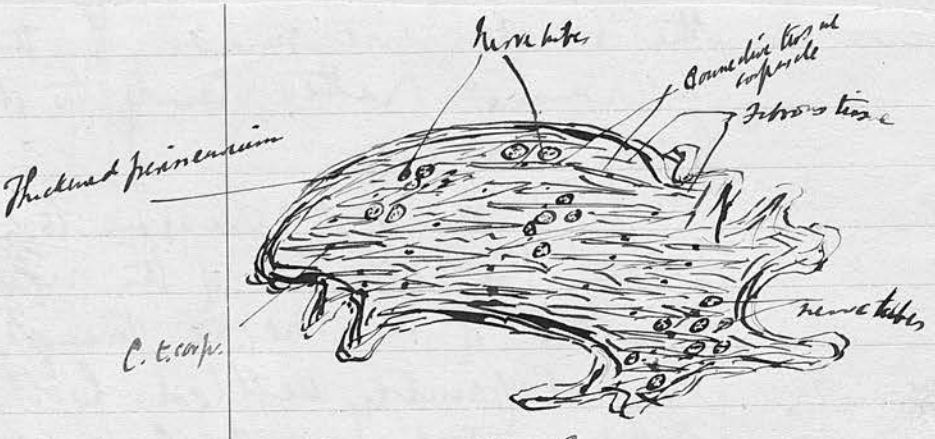
The trunk of the sympathetic is intact, but its branches are invaded by myxomatous tumours. There were two nodosities on the intestines. The patient died from tuberculosis which is very common in individuals affected with neuromata (sic)".

The foregoing report, as we have stated, is thus seen to form a very interesting supplement to von Recklinghausen's report, though the careless use made of the word "neuromata" rather tends to detract from its value.

As I had occasion to mention before, the question of the origin and structure of the nerve tumours is very definitely settled, both among continental and English observers. Among the latter it would be well to refer to the observations of Payne[1] who has given a great deal of serious attention to the subject. Speaking of the nerve tumours removed from an

1. J.F.Payne. Trans.Path.Soc.Lond., Vol.38., p.69.

Opposite Page 107.



Micros. view of a small neurofibroma, atlas Pl. 1.

Note the thickened perineurium, and the peculiar increase of the connective separating the nerve fibres so that a fibrous tumor is produced.

undoubted case of generalised neurofibromatosis.

He says :-

"The smaller tumours appear before dissection, in some cases, as if they might be swellings of the nerves, but the more minutely they were dissected, the more they appeared to be outside the nerve bundles and to be connected with the perineurium and the interfascicular fibrousitissue. This condition was confirmed by the microscopic examination of one of the smallest of the tumours, of which transverse sections were made by Mr. Shattock and of which one is represented in Figure(see opposite).

These sections were stained with Osmic Acid and with Logwood; the former reagent did not colour the structures uniformly, probably owing to the imperfect preservation of the specimen, which not being intended for microscopic examination had been kept in weak spirit, but in the section coloured with logwood numerous sections of nerve tubes are seen scattered through the fibrous tissue and especially accumulated on one side of the section. The remainder of the tumour consisted of nucleated fibrous structure precisely like that of an ordinary fibroma and clearly

originating from the connective tissue of the nerves. There was no appearance of new formation of nerve tubes, but if anything, rather a wasting of these structures. The whole tumour was then as in other specimens of this kind a fibroma of nerves or neuro-fibroma."

So much then for the swellings found on the nerves; but what does the same observer say in regard to the cutaneous tumours? Here is his report, which is a continuation of the preceding:-

"Sections were made of several portions of the skin taken from the chest and the left arm, containing small molluscum growths, and stained with Osmic Acid and Logwood. The appearances were as follows:- The epidermis was seen passing over the tumour quite unbroken, and presenting no notable thickening or other change. Over the tumours the papillae and inter papillary processes were not well marked, but otherwise the epidermis was normal. There was a well marked pigment layer, in some parts very thick. The tumours themselves consisted of fibrous connective tissue with numerous nuclei. The fibro-nucleated growth evidently started from the corium and from its deep layers.

There was a zone of fibrous tissue immediately under the Malphigian layer of epidermis in which few nuclei could be seen. Thus the papillary layer was comparatively unaffected. The new growth was formed by bundles which passed upwards from the horizontal strands in the deep part of the corium, and projected above the level of the skin, carrying the unchanged epidermis with them. They extended horizontally to some extent, and were continuous with collections of nucleated tissue around certain structures of the skin about which normally the connective tissue is thickened, especially round the sweat glands and ducts, and to a less extent around the sebaceous glands and hair follicles. There was very little accumulation of nucleated tissue round the blood vessels, and the growths were not at all perivascular as is the case with infective granulomata of the skin. The relations of the growths to the nerves were carefully observed. Nerve fibres were seen in a few specimens when stained with Osmic Acid; but their sheaths were not thickened or altered and they had no special connection with the new growths.

While the growths generally might be considered

as starting with an overgrowth of the corium generally at certain spots, there was in some specimens a more definite connection with the fibrous sheaths of the sweat glands and their ducts.

In some minute tumours the outline of the duct of the sweat gland could be seen running through the very centre of the tumour, the duct being surrounded by nuclear infiltration which was continuous with the growth, there was also a similar collection of nuclei with fibrous hyperplasia among the convoluted tubules of the gland itself. Here the commencement of the tumours, instead of representing the papillary hypertrophy was ratherinter-papillary. In larger tumours, which would include the areaof many sweat glands and papillae these relations were naturally not well marked. Hair follicles and sebaceous glands were in several instances included in the growths. The hairs were abortive or represented by plugs of a morphous matter as was observed also during life, when sebaceous plugs or comedones were seen to be scattered irregularly over some of the tumours, and evidently were not their starting point, though there were sometimes, as has been said, a little fibro-

nucleated overgrowth around them. Nothing could be said about the relations of the lymphatic vessels or spaces. The tissue was so much contracted by the action of the spirit as to appear very dense, but it was evidently much lower in its consistency during life. Pacinian or touch corpuscles were in two instances seen, but had no special relation to the growth."

Such is Payne's report, and it is a good one. It bears upon its face the stamp of careful honest work; but apart from that, we have only to place it side by side with von Recklinghausen's to have our interests keenly aroused; indeed there is a certain element of humour in the comparison, if I dare to say it. Analyse the two reports, and what do we find? That the two writers have observed practically the same thing, and where they differ is in the interpretation of the evidence obtained under the microscope and the amount of importance each is willing to attach to the individual facts observed.

Von Recklinghausen, having made out a hyperphasia of the connective tissue sheaths of the nerve trunks in the subcutaneous tumours sees a nerve or two

in a cutaneous tumour and says "Here we are; these tumours are undoubtedly the same as those on the nerve trunks, the new growth takes its origin from the sheaths of the nerve fibres; see here the nerve fibres are quite plain; this is a neurofibroma. It is true there is also an apparent fibrous development around the sebaceous gland; the same thing is even more apparent around the sudoriparous glands and their ducts, why the fibrous overgrowth even uncoils the glands, while in some of the tumours I really cannot find any nerves, but that is quite unimportant, the nerves were there once, but they are brushed out now; the implication of the grit glands and their ducts is a mere accident this IS a neurofibroma".

Payne on the other hand retorts: "OH, yes! I see your nerve fibres very well - in a few specimens - but it is plain they have no special connection with the tumours. Why, their sheaths are not even thickened, but just look at these sweat glands and their ducts; do you see them? The connection between them and the origin of the growth is perfectly clear, isn't it? You see for yourself the sweat duct running

through the very centre of the tumour, plainly showing that the growth was developed from around it".

But the opinions of these two observers do not represent all the views on the subject. Lahmann[1] in his record of two cases quoted by Max Jordan[2] observed in his first case that the connective tissue sheaths of the blood vessels, the sebaceous glands, and the sudoriparous glands were the seats of origin of the hyperplasia.

In his second case the fibrous new formation began from the sheaths of the nerves. He therefore made the following classification:-

1. Fibromata arising from the sheaths of the nerves.
2. Fibromata arising from the sheaths of the blood vessels.
3. Fibromata arising from the connective tissue sheaths or the sudoriparous glands and sebaceous glands.
4. Fibromata of mixed origin.

Max Jordan[3] himself in the two cases of Congenital Elephantiasis, (aspect of generalised neurofibromatosis) which he examined after amputation

1. Lahmann. Die multiple Fibrome in ihrer Beziehung zu den Neurofibromen. Virch.Archiv,t.101.
2. Max Jordan. loc.cit. p.73.
3. Max Jordan. loc.cit. p.71.

of the limbs involved made out an increase in the volume of the nerve trunks at the seat of the lesions. This increase of fibrous tissue was uniform in his second case, but nodular in the first. In both cases however, the new formation of connective tissue seemed in some parts to have an independent origin, while in other parts it seemed to take its rise from the peri-fascicular or the intra-fascicular tissue of the nerves and on closer examination he observed that it was from the blood vessels of the connective tissue named that the proliferation actually started. THis conclusion based on these observations was that the growths were angiogenètic tumours of the nerves. In regard to the skin tumons with which we are now more immediately concerned, Max Jordan made out that in a similar manner the new formation also began from the connective tissue of the blood vessels, not only those pre-existing but newly formed ones as well. Hence he concluded that the minute anatomy of these growths indicates that the cases he observed are to be classified as follows:-

Diffuse angiogenetic fibromatosis of the skin, the subcutaneous connective tissue, the large vessels,

the peripheral nerves, the muscles, with multiple subcutaneous angiogenetic fibromata, and angiogenetic fibromata of nerves. At the close of his monograph, however, he admits the occurrence of a hyperplasia beginning in the connective tissue proper of the nerve sheaths (not of the blood vessels). He then states that congenital elephantiasis may be divided into two kinds:-

1. Fibromatosis of nerves.
2. Angiogenetic fibromatosis of various structures, including subcutaneous connective tissue, nerves, large vessels, and muscles.

In point of fact, he does not much insist upon the first variety, and as one observer has stated, the admission seems to have been made more as a compliment to von Recklinghausen, than from Max Jordan's own conviction.

In support of his angiogenetic theory, Max Jordan[1] quotes Philippson[2] who expresses the belief that a case observed by him also belonged to the angiogenetic variety, and not only that, but in none of the tumours examined by him (Philippson) could he

1. Max Jordan. loc.cit. p.76.
2. Philippson. Beitrage zu Lehre von Fibroma Molluscum. Virch.Archiv. t.110.

find a single nerve fibre. This of course is quite opposed to the opinion of von Recklinghausen, who as we remember, expressly stated that he could not get any evidence of the growths starting from around the blood vessles. Among the few British authors who have published the result of any work on the subject, we must quote Hilton Fagge[1] who has given a certain amount of attention to the subject.

"The conclusions arrived at by Mr.Houre and myself as to the nature and of the seat of origin of molluscum fibrosum are as follows:-

1. That each tumour is originally developed around a hair follicle enclosing at the same time a sebaceous gland belonging to the hair follicle.

2. That the smaller tumours consist of two distinct elements:- a central glandular body, itself surrounding a hair; and a peripheral mass of very fine connective tissue containing numerous minute oval nuclei.

3. That the glandular body is a sebaceous gland enlarged by the separation of its sacculi from one another and perhaps also by the actual multiplication and increase in size of the sacculi themselves. The

1. C.Hilton Fagge. On the Anatomy of a case Of Molluscum Fibrosum, Med.Chir.Trans. Lond. VolLIII. June 1870.

latter supposition is founded mainly on my own observations made by flattening the smallest tumours en masse.

4. That the peripheral mass of nucleated connective tissue is developed from the two external layers of the dermal coat of the hair follicle and sebaceous glands. This point appears to be conclusively established by Mr. Houre's observations which he has given me the opportunity of confirming. The only difficulty which stands in the way of the above theory is that in some cases the tumours appear certainly to be developed in positions in which sebaceous glands are not known to exist."

Although this is they"only" difficulty it is a very serious one nevertheless, and we should imagine quite sufficient to convince Dr.Fagge that his theory at best can only be partly true, but he attempts to explain away the difficulty, by drawing attention to the fact that tumours on the palms and soles were only of rare occurrence. They certainly existed in one of Payne's[1] cases(Jesse F., aet 64). As regards the tumours which are sometimes found on the mucus

1. J.F.Payne. Clin.Soc.Trans. Vol.22, p.189.

membrane of the hard palate where, of course, there are no such things as sebaceous glands, Fagge ventures to suggest the probability the growths are developed around glands in the mucus membrane in the same way as the cutaneous growths around the sebaceous glands!

In a matter of this kind a single grain of fact is worth all the probability that it is possible to suggest, and this statement of Fagge is not, in my opinion, in itself worthy of any serious consideration. A reference to the observations of Lionel Beale[1] will show that even as far back as the year 1855 views were held on the subject destined to be entirely contradictory to those of Fagge. Beale's conclusions were as follows:-

1. That neither the sebaceous glands nor the sweat glands nor their ducts were concerned in the formation of the tumours.

2. That the tumours consisted essentially of a morbid alteration of the structures concerned in the formation of the hair, especially if the cells at the deepest part of the follicle and of the follicle it-

1. Lionel Beale. Trans.Path.Soc.Lond. Vol.VI.,p.313.

self.

3.T That the subcutaneous areolar tissue was considerably hypertrophied both its white and yellow elements being coarser and more abundant than in health."

Following upon Beale's paper we find several German authors, among whom we must notice Professor Fŏrster, expressing views utterly opposed to both those of Fagge and Beale. In 1858, three years after the publication of Beale's paper, Prof.Fŏrster[1] published a monograph in which he expressed a view that the tumours all consisted of fully developed connective tissue and were clearly seen to be circumscribed growths of normal tissue elements of the deeper layers of the cutis.

That the growth was in continuity with surrounding parts and not simply embedded in them. In the skin covering the most minute of the tubercles, there existed a small dark point resembling a comedo, but this was due to the fact that some of the tubercles developed themselves round or beneath hair sacs and

1. Forster. Ueber die Weichen warzen und Mollusken artigen Geschwlste der Haut. Wein Med. Wochenschr. 1858.

as they gradually increased in size pushed the hair and its sebaceous glands upwards to one side or inverted them entirely."

It is worthy of note that after the publication of Förster's monograph Beale was so convinced of the correctness of those views that he publicly acknowledged that while he considered the observations made by himself true for his own case, he did not believe that they necessarily applied to all cases of the same disease. Sangster[1] is another English observer who published a case of molluscum with engravings and histology. His views are similar to those of Fagge. But Unna[2] who is completely of von Recklinghausen's opinion is not very tolerant in regard to the views of Lahmann, already discussed, and with the latter he includes Fagge. Referring to this subject Unna says "Lahmann's chief case upon which he founded his futile critique of von Recklinghausen's views and his own theory corresponds neither clinically nor histologically to the neurofibromata, but probably to the

1. Sangster. Clin.Soc.Trans. Vol.XIII. p.166.
2. Unna. The Histopathology of Diseases of the skin, translated by Norman Walker, 1896. Chapter on Neurofibroma, p.844.

simple fibromata as does probably the analogous case of Hilton Fagge."

Later on he goes on to say "In true neurofibroma there are no degenerationsoof the epithelium and the epithelial appendages. The regular cystic degeneration of the hair follicles in the centre of the tumour described by some authors (Hilton Fagge, Lahmann) show on other grounds that the tumours were not neurofibromata, but polypoid naevi or some other form of fibroma."

Kriege[1] who published an essay on the subject is entirely of von Recklinghausen's opinion. (It may be mentioned in parenthesis that Kriege was von Recklinghausen's assistant) and Unna[2] bearing testimony to the accuracy of Kriege's work states that "Kriege very carefully investigated the relations of the cutaneous nerves and the cutaneous tissue in the formation of neurofibromata and after examining three cases of my (Unna) [3] own I can fully confirm his statements."

1. Kriege. On the relation of the nerve fibres in multiple fibromata of the skin and neuromata. Virch. Archiv, 1887, Vol.8.
2. Unna.Loc.cit.
2. Unna. loc.cit.

Unna's investigations are of special interest in this that they led the author to the conclusion that neurofibromata contains certain cells which were characteristic of them. His conclusions are stated as follows:-

"The most striking constituent of neurofibroma is the mast cell, (mast zellen) and a peculiar variety of it. These also are pretty regularly distributed over the new formation. In the larger nodules they are present in quantity and in greater abundance than in the surrounding cutis where they only accompany the vessels in somewhat increased numbers. In the small nodules they are still less numerous; in the nodule, but pretty abundant in the immediate neighbourhood. We see first ordinary mast cells which stain with Polychromic methyl blue, show in addition to a small blue nucleus the deep red granules collected in a regular dense oval halo. But even within a low power we see in some nodules in addition to a few ordinary mast cells others surrounded by a large red halo about double the size of an ordinary mast cell. This halo shows the same red colour as the

granules, but, as a high power shows, is not granular but very finely spongy.

It is therefore a spongioplasm, peculiar to the mast cells, staining like the granules. A thorough investigation of these cells shows that they surround the central nucleus asymmetrically. In some cases processes of protoplasm extend around the latter structure and meet on both sides, so that it is partially but not completely covered by a mantle. In other cases the red halo only has the form of an irregular plate giving off thread like processes in different directions, and only lies alongside the mast cell if we restrict the term to the nucleus and granules. The cells thus recall the winged cells of tendons. In other cases again we see a bell, or jelly fish shaped, spongy mass, with veil-like processes in whose cavities the nucleus and its granules lie. Evidently we are dealing with a wide spread mucus change of the connective tissue cells which is quite peculiar to the neurofibroma and must be borne in mind in the diagnosis of this tumour."

These mast cells, if really peculiar to neurofibromata would certainly form a most valuable diag-

nostic factor, but no other author so far as I know, has been able to confirm Unna's statements in this regard. Only a few weeks ago, after listening to a very interesting lecture on Phagocytosis by M. Metchnikoff at the Pasteur Institute, in which mast cells were freely discussed I took the opportunity of asking M.Metchnikoff his opinion on these peculiar mast cells of Unna. He replied that mast cells diapedesed as other leucocytes did, and he had found them everywhere in the tissues; but that he had never met with this particular variety of Unna, and he did not see how any mast cells could be specially related to neuro-fibromata. It is to be regretted that Unna's position on the subject is not stronger for a special mast cell would be as good as a specific organism in simplifying the diagnosis of the condition.

Westphalen[1] another authority cited by Max Jordan states that in a case examined by him, no glands, but only nerve fibres were found in the tumours.

Brigidi[2] following von Recklinghausen, is of

1. Westphalen. Multiple Fibrome der Haut und der Nerven mit Uebergang in Sarkom und mit Melastasenbildung. Virch. Archiv, t.110.
2. Brigidi. loc.cit.

of opinion that the cutaneous fibromata always take their origin from the nerves but that sometimes this fact cannot be made out on account of the very small number of fibres which the tumours are apt to contain. Brigidi also reported the presence of small neuro-fibromata completely analogous to those found in other parts of the body, in the muscular tissue of the Biceps and of the left thigh. No other author, so far as I know, has recorded a similar observation.

Psomorski[1] quoted by Max Jordan[2] states that in his case the tumours of fibroma molluscum proceeeded equally from the sudoriparous glands, the hair follicles, and the nerves.

Crocker to whom I am personally indebted for the references to Payne's cases and his own work[3] on the subject is of opinion that "On the whole it is probable that hyperplasia of all or of any of the structures (in the skin) may occur, and that we are not justified in restricting it to one structure only." According to the same author Virchow refers the origin of the growth to the connective tissue of the fat,

1. Psomorski. Ein fall von Ranken neurom der intercostalen nerven mit Fibroma Molluscum und Neurofibromen. V.A. t.108.
2. Max Jordan. Loc. cit. p.75.
3. Crocker. Diseases of the skin, 2nd Edit.p.587.

but it appears that the latter's experience on the subject had been limited to the examination of a few tumours removed biopscally from a case which came under his observation.. In a case examined by Lantzenberg for Feindel[1] two adjacent tumours were removed from the skin of a patient suffering from generalised neurofibromatosis; these tumours were selected on account of their small size, for, Feindel following out von Recklinghausen's theory of the crushing out of the nerves in a late stage of the growth, considered that he was more likely to find out the true nature of the growth if he examined it in a very early stage of its development. The preparations made were stained with Logwood according to the method of Wiegert, and each nodule was observed on examination to contain a nerve and further, what from Feindel's point of view, was a fact of extreme importance, so important, indeed, as to settle once and for all the exact point of origin of these fibrous overgrowths was that each nerve occupied the very centre of the nodule, but of course, it will be remembered that this is nothing else but a condition exactly similar to what Payne

1. Feindel. loc.cit. p.49.

observed in regard to the sweat ducts.

And now I shall be asked "Why have you lead us through this maze of wearisome quotations? Why have you not exercised your judgment, and selected the correct view, if any, and submitted it to us? Indeed, have you yourself any opinion on the subject?" My reply is that these quotations are not as tedious as they would appear. The views expressed in them are full of interest and instruction. They teach us as perhaps few other examples in Medical Science can, how it is possible for competent observers to differ on such a restricted piece of minute anatomy as that of small cutaneous tumour. In the attempt to localise the seat of origin of these growths no view which is reasonably, or I might add, unreasonably, possible to advance, is wanting from the long list I have cited. We see this origin attributed to each organ in the skin individually, we see it also attributed to various combinations of these organs; we see it again attributed to all the organs collectively and, finally, we have the view of Dr. Pierre Mariel[1], a

1. Marie. Loc.cit.p.274.

man of the keenest observation and whose opinion must always carry the greatest weight, that from the evidence obtained in the cases examined by him he is unable to attribute the origin of the tumours either to the nerves, the glandular organs, or the blood-vessels. That is to say, that they appear to take their origin indiscriminately in the tissues of the skin. M.Darier quoted by Hallopean[1] is exactly of the same opinion.

Was there ever a better instance of the aphorism"Quit homines tot sententiae?"

I have not given preference to any of the views stated; indeed I did not set out to do so, and if I did, you would not agree with me.

The observations in question have all been made by responsible men and they are to be considered correct, but - and this is the point - only in so far as they relate to the particular specimens from which they were made. It is when an attempt is made to generalise from particular observations, to reason too closely by analogy, or to indulge in more or less.

1. Hallopean. Neuromes multiples. Annals de Dermatologie, 1889. Nos.8 & 9.

far fetched speculations that our authors become hopelessly at fault, for it is obvious from what has preceded that the cutaneous tumours in this disease are not all of the same nature. We have seen that they may take their rise from any of the organs in the skin, and of these the connective tissue sheaths of the nerves, and those of the coil glands with their ducts would appear to be most often selected, or the growths may arise independently in the connective tissue sheath of the corium, or in the subcutaneous tissue.

These are, in fact, the only real conclusions that it is possible to draw from the Babel of opinions I have cited - opinions which singly are of restricted value, but united serve the useful purpose of a basis for arriving at what appears to be necessarily the true solution of the difficulty.

But we have not yet quite finished with the question of new growths, we have still the neurofibromata which von Recklinghausen, as we have seen, diagnosed in the walls of the stomach and intestines of Marie Kuntz. We recollect that he was unable to make

out the connection of the nodules in the stomach with any of its nerves, the difficulty as he stated, being in the amyelinic nature of the latter, but that in the intestine he found certain cells in a fibrous nodule which he considered to be the atrophied ganglionic cells of the myogastric plexus. Besides von Recklinghausen, no other author, so far as I know, has published any observations on gastric and intestinal neurofibromata except M.Albert Branca, who performed the autopsy and conducted for Dr.Marie the histological examination of the specimens taken from the body of our patient Guillaume. I am personally indebted to Dr.Branca's kindness for a copy of his report on the case published in the Bulletine de la Société Anatomique, Février, 1897.

Guillaume, as we remember, did not present any subcutaneous tumours for examination during life, and P.M. after a careful search along the nerves of the limbs, the neck and the thorax, no enlargements could be found. On examining the intestines, however, in addition to extensive tubercular ulceration, they presented several nodules especially in the deep

parts of the mucus membrane. These nodules on examination proved to be pseudo-neuromata. On section their surface was rounded, oval, or reniform, and their long axis in certain cases parallel to the surface of the mucosa. The lamellar sheaths of the nerves found in the nodules were thickened and composed of concentric layers of tissue pressed against each other. In some places the sheath appeared to split itself into two concentric lamellae which were either completely separate from each other or which fused together at one or two points. In the space between the separated lemallae capillaries and newly formed connective tissue were observed. This fact Branca thinks is of great importance as it points to the probable seat of origin of the fibrous hyperplasia. The nerve elements were composed of fibres of Remak in some places and of fibres and ganglion cells in others. They showed no preference for a central position in the growths and were most usually eccentrically situated in the tumour mass and in contact with the inner lamella on the connective tissue sheath.

Branca thinks that von Recklinghausen's obser-

vations in regard to the "ganglionic cells of the myogastric plexus" need confirmation.

"It is not in accordance with the teachings of general pathology" he says "that the ganglion cells should survive after the nerve fibres have been crushed out, seeing that the former are much more vulnerable than the latter". A very forcible remark we observe, and one with which I fully concur. At any rate Branca's observation fully establishes the occurrence of intestinal neurofibromata in a far more conclusive manner than von Recklinghausen, and for us it has this special significance that it confirms the diagnosis of generalised neurofibromatosis made during Guillaume's lifetime in spite of the fact that no tumours could be made out along the subcutaneous nerves of his body. As Branca says in concluding his report "Our autopsy in which we find side by side the grains of molluscum (cutaneous dermatofibrosis) and the lesions of the nerves of the intestines (intestinal neurofibromatosis) shows sufficiently well the multiplicity of forms under which pigmentary fibromatosis may appear, it justifies us in asking the question whether there does not ex-

ist exclusively visceral neurofibromatoses in the same manner as exclusively cutaneous neurofibromatoses" This is certainly a valuable hint to most of those who are in the habit of performing post-mortem examinations to examine in every case, the intestines, the latter as we know, being frequently neglected owing to the unpleasantness associated with its examination. We may mention that the diagnosing of Pulmonary Tuberculosis was also confirmed by the appearance of Guillaume's lungs and his liver and kidneys showed in a marked manner the result of his alcoholism.

Brigidi[1] who has worked out the histology of generalised neurofibromatosis with great care says that in an autopsy which he made "the sympathetic showed itself in its entire course from the cervical to the lumbar region to be thicker than normal and of a somewhat fibrous character."

"The cervical and semilunar ganglia " he went on to say "were worthy of note on account of their pale and swollen condition".

1. Brigidi. Monatschefte fur prakt Dermatol. 1894, 1st Sept. No.5, p.194.

We now, in concluding the anatomy and histology of the lesions in this disease, pass on to the pigmentation and it is to Brigidi[1] again, who has done such excellent work on the subject, that we owe our knowledge of the histology of the pigmented spots & patches.

The pigmentation , he says, is caused by the presence of deep yellow and even black granules, abundantly scattered in the protoplasm of the malphigian cells, more especially those which normally contain granules of pigment. The brown spots in the papillary layer of the corium, he also states, are due to a deposit of pigmentary granules in the bodies of the connective tissue corpuscles, so that the latter greatly resemble the pigment-bearing cells occurring in the connective tissue of the frog; a few pigment granules were also found freely scattered between the fibres of the papillary bodies.

From what has preceded we are now pretty well acquainted with the symptoms and progress of the disease which is engaging our attention. We have seen that it may come on at any age, though most frequently it is congenital, or at any rate it begins early in

1. Brigidi. Loc.cit. 197.

life. The different modes of commencement have already been fully entered into. In the cases that are apparently not congenital we often notice the disease coming on after some malady such as an infectious fever or even after an injury as has been indicated. In a case quoted by Feindel[1] the first crop of tumours appeared in a woman who was born with "coffee and milk" coloured spots at the age of 17, after a confinement.

In some cases the appearance of the lesions is preceded by headaches, vertigo, shooting pains in the limbs, cramps, sensations of numbness, and other nervous manifestations. The pains just mentioned must be distinguished from chronic rheumatism which is not uncommon in the subjects of generalised neurofibromatosis.

The tumours are not as a rule painful, but in some instances they give rise to great discomfort. In one of Bayne's cases a large tumour in the left axilla was accompanied with intense neuralgia of the whole of the left arm. As a rule, however, the symptoms do not appear to bear the least proportion to

1. Feindel. Loc.cit. p.61.

the extent of the lesions. We have already dwelt on the principal sites of the tumours; they may be found all over the body though rarely on the palms and soles As a rule they are more confluent on the trunk and the cephalic extremity of the body. They are not usually plentiful on the limbs, and less so near the extremities of the latter than towards the roots.

The physical appearance of the tumours and spots has already been described. Most commonly we find tumours of the subcutaneous nerves accompanying those of the skin, but not in all cases. We remember that in Guillaume's case there were no subcutaneous tumours to be made out. In other cases the tumours along the nerves are present, but it is the cutaneous tumours that are altogether absent. Launois and Variot quote an instance of this kind. These cutaneous tumours may be present in large numbers all over the body or they may be very few: the same for the pigment spots and patches. Sometimes the pigment is not distributed in spots over a large area, but in one diffused sheet. The spots have not, so far as I know, been made out on any mucus membrane, as in Addison's disease, but we know .

that the tumours have been found on the hard palate and on the gastro intestinal mucus membrane. The mode of distribution of the spots and their direction have been already fully entered into. We remember the frequent occurrence of vascular and piliary naevi along with the spots and tumours. Sometimes, as we have seen, the first sign of the disease is the appearance of a "major tumour" which may remain indolent for many years and then suddenly, without any apparent cause, or following upon some disturbance of the system, take on a rapid growth, the smaller tumours at the same time making their appearance. We must mention that in structure the "major" tumours are merely an exaggeration of the smaller fibromata; there is no essential difference between them and the smaller growths. The thyroid gland, as we have seen in Herczel's cases, may show nodosities, the significance of which, however, has not been determined. In some cases the patients do not appear, apart from the disfigurement and mechanical inconvenience, to be any the worse for the presence of the tumours. A notable instance of this kind was observed by Robert Smith[1]

1. Robert Smith. A Treatise on the Pathology, Diagnosis and Treatment of Neuroma. Dublin 1849.

and published along with some other cases in a large book containing a set of really magnificent plates which should be studied by all those who take an interest in generalised neurofibromatosis. The particular case I refer to is that of John M'Cann aet 35, who was admitted into Richmond Hospital in 1840. He had a large tumour on the right side of the neck (I have had Robert Smith's lithograph of this patient reproduced by a clever artist from a rough sketch made by myself in the library of the British Museum where I consulted Dr. Smith's work. It will be observed that the sites of the tumours are correctly reproduced. In Dr. Marie's book[1] they do not correspond with the original, a fact which I pointed out to Dr. Marie himself) of a globular form, and equal to a moderate sized cocoanut in magnitude. It extended from the mastoid process to within a short distance of the sterno-clavicular articulation. It presented a uniform surface, and admitted being moved freely in every direction, but could be neither pushed upwards nor drawn downwards; the external jugular

1. Marie. loc.cit. p.265.

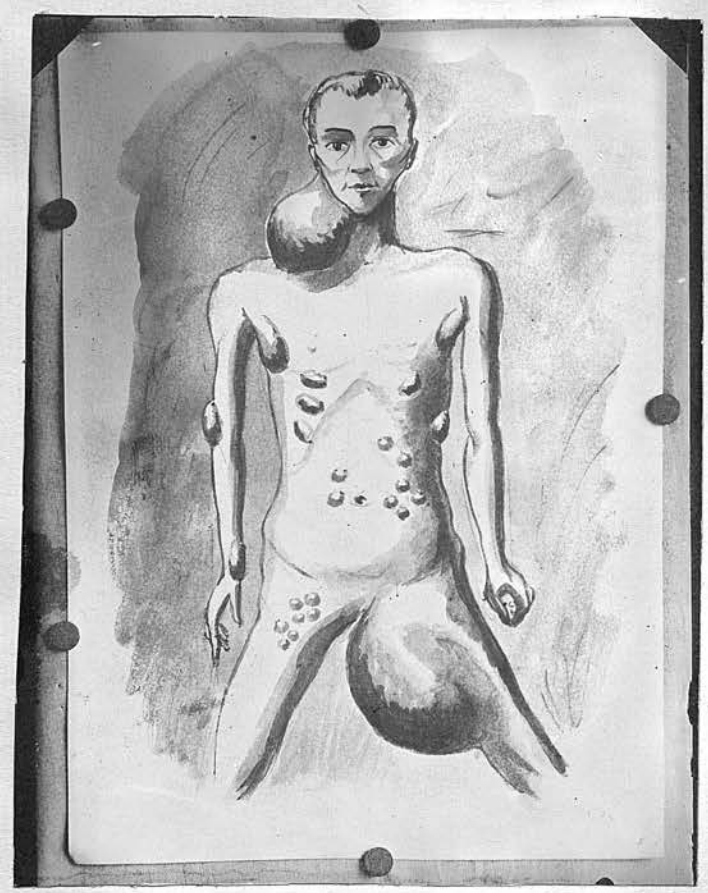


Fig.XIX. John McCann. Case of generalised neurofibromatosis with enormous "major" tumors. After Robert Smith. The large tumor in the neck is connected with the Right Vagus, and the other large one on the thigh with the left sciatic nerve.

vein grooved its surface, the integument did not adhere to it nor (although it obviously extended deep into the neck) did it appear to have contracted a close adhesion to any important part. The larynx was not displaced nor was there any interference with the functions of respiration or deglutition. It was solid throughout and had existed for upwards of 15 years; but had never been painful, nor was it now (although of so large a size) a source of much inconvenience to the patient whose general health was not impaired. A second tumour about as large as a walnut existed under the left side of the tongue, solid and free from pain; but its presence annoyed patient greatly when eating. He could not tell when the tumour had commenced to form, being unaware of its existence until it began to interfere with the motion of his tongue"!

A reference to the accompanying photograph will better indicate the enormous size of the growth in the neck and another one which subsequently appeared on the left thigh, and make us wonder at the remarkable lack of serious symptoms which the patient exhibited, at any rate up to a certain time.

In a large number of cases, however, the muscular pains, the vertigo, the headaches and neuralgias, the arthralgic pains etc. compel the patients to take to their beds. Various disorders of cutaneous sensibility including vague hyperaesthesias and anaesthesias are apt to supervene the latter putting the patients in danger of burning themselves. After a time physical and other central nervous disturbances are apt to come on and finally the peculiar cachexia of the disease, so well exemplified in Flond's case, manifests itself. This last condition has long been recognised and most of those who have studied the disease, have drawn attention to it.

In Robert Smith's[1] case already quoted, three years after the patient came under observation, his condition is thus described.-

"He was now pale and greatly emaciated, had no relish for food and did not sleep; never complained of any particular distress, nor could he assign any cause for his restlessness; he had neither diarrhoea nor perspiration. Pulse quick and weak, but respiration undisturbed. He lingered for a few months,

1. Robert W. Smith. loc. cit.

pining and wasting away, and towards the end of the year (1843) he died with hectic symptoms and without pain, but terribly emaciated."

Speaking of one of his cases Dr. Payne[1] says "the examination of the thoracic and abdominal organs showed nothing of importance, except the existence of some empysema of the lungs, and a little bronchitis. At first a little albumin appeared in the urine, but that disappeared. The temperature was quite normal. It must, however, be insisted upon that the patient was decidedly ill and cachectic, displaying a degree of weakness quite out of proportion to any organic lesion discovered".

* Landouski has also noticed a similar state of things. In reference to this condition he says.-

"Walking is distressing; the least movement a veritable labour; every mental effort a fatigue. The expression is stupid, the body more or less undermined, emaciated, stunted".

Reference to the same state is thus made by

1. J. F. Payne. A case of the Muscum Fibrosum. Clin. Soc. Trans. Lond. Vol.22, p.189

Rumen[1] in his thesis - "the pain as we have said in generalised neuromata is nearly always insignificant, but if the symptoms are accentuated one is at once struck with the well marked and serious alterations in the general health. Owing to grave disturbances of nutrition brought about by this nervous affection the patients fall into a state of marasmus and exhaustion. They are emaciated and bloodless and they present an utterly prostrate condition, combined with excessive restlessness and a distressing insomnia. In this stage the disease does not take long in coming to a fatal termination, and the patient succumbs in from five to six months from cachexia and exhaustion.

In 1893 Reynolds and Collier publised an interesting case of the disease showing the points we are now dealing with. It was that of a man aet 26. - "Patient complained of general weakness and since at the age of 16 he had remarked the presence of small tumors disseminated all over his body. He had lost by degrees all power of voluntary movement except as regards his head, the right fore arm and

1. Rumen. These de Paris 1875, p.42.

the respiratory muscles. He had no disorders of sensibility nor paralysis of the bladder nor of the rectum. He was very emaciated and it were possible to see and to feel innumerable tumours varying in size from a small apple to a pea, in every part of his body. He died of exhaustion.

P.M. all the nerves of the body, including the sympathetic down to their small branches had tumours upon them. In the interval between successive tumours upon the same nerve, the calibre of the latter was greatly increased; the anterior roots were also affected inside the spinal canal, but within the cranium the cranial nerves were healthy".

Groh[1] published a case with two plates in which a young woman, aet 26, suffering from generalised neurofibromatosis died of Marasmus".

Launois and Variot[2]'s description of the condition is full of pathos. "The third period is one of cachexia and marasmus; the patient wastes away; he completely loses his appetite; sometimes he suf-

1. Groh. Ein fall von Fibroma Molluscum. Wein.Med. Blatter. 1888, No.4.
2. Launois et Variot. loc. cit. p.422.

fers from sickness nor from diarrhoea. A condition of extreme emaciation supervenes which renders the tumours still more conspicuous. Sleep becomes impossible, either on account of the violent headaches or from the constant jerking of the limbs. The pulse is small and rapid; the skin and the mucus membranes are discoloured. All the functions are thrown into abeyance and a fatal termination comes after a more or less protracted period, varying with the resisting power of the organism. The patient dies from exhaustion for P.M. nearly all the organs are found unaffected.

Sometimes the patient falls into a typhoid condition before death."

Follin[1] has made similar observations and he tries to give a reason for the condition. "The grave disturbances of nutrition which characterise the neuromatous diathesis (sic) would be perfectly intelligible according to our explanation if future observations permit the general application of Lebert's observations on the disappearance of the ganglionic nerve

1. Follin. Triate de Pathologie externe, Vol.II. p.223.

cells. The great sympathetic (splanchnic) having a nutritive function, the latter ought to cease or at rate be seriously impaired when that ganglion is affected.

The cause of this disappearance of the ganglionic cells is due to nothing else but a hypertrophy of the neurilemma crushing out the tissue proper of the ganglion just as the hypertrophy of the fibrous tissue of the uterus is seen to obliterate the parenchynea of that organ, and similarly in the prostrate gland; but due importance must be given to the condition under which the patient's life, mainly, compelled to remain in bed and frequently enough deprived of air and light."

We notice Follin's dogmatism and his tone of "the man who knows" but we are not much impressed. We ourselves can speculate; we ask for facts not hypotheses.

In some cases the mental symptoms are well marked. It will be remembered that Guillaume had at one time to be confined in a lunatic asylum. Hebra as we have seen, lays great stress on the weak in-

tellect of individuals suffering from this disease. Dr. Payne referring to a case said that the individual had the physical characteristics of a cripple and was certainly of low intelligence, though able to earn her living and go through the ordinary duties of life. He also said that his attention had been drawn by Dr. Barlow to a family of children several of whom were affected in the same way and who are almost idiotic and show progressive weakening of the intellect. Sometimes the nervous manifestations include fits which though of a more or less epileptiform character, may still be of a hysterical nature. It will be remembered that Guillaume used to take fits the true nature of which was not determined. M.Marie is inclined to the belief that they were hysterical rather than epileptic.

Claus[1] published a case of "generalised fibrolipoma", but which from the description looked rather like a case of generalised neurofibromatosis, in which the patient was subject to epileptiform fits.

In cases where the mental symptoms are not so pronounced we commonly have an impairment of memory

1. Claus. Flandre Medicale, 1895, No.20, p.609

and of the special senses. The superficial and deep reflexes are also frequently exaggerated or otherwise impaired.

As a rule when the patient is lying quietly in bed he suffers little pain, but nearly every movement, especailly those of the limbs causes him intense suffering. Flond could not bear to be touched at all and even when he was getting out of his bed to be photographed he preferred to climb down in his own fashion, rather than have anyone to assist him by holding any part of his body. Sometimes rheumatismal pains are superadded to those of the disease, a fact to which von Recklinghausen[1] has called special attention. Attempts to walk are followed by cramps, tremors, feelings of numbness, or shooting pains in the lower limbs. There is not usually any paralysis though in one of Launcis and Variot's cases there was a well marked puraplegia. In some instances says Dr. Marie the limbs of both extremities are paralysed. Lancis and Variot also quote a case in which towards the end there were symptoms of medullary compression

1. Von Recklinghausen. loc. cit. p.66.

Such are the main features of the course of the disease which as a rule progresses slowly up to a certain stage which Launois and Variot call the third period. Not unfrequently complications set in, either in the form of Tubercular Phthisis which helps to carry off the patient or an obstinate diarrhoea often accomplishes the same thing. Sometimes the tumors usually the "major" ones undergo sarcomatous degeneration, as in Cimmino's[1] case where a large tumor in the sacral region became malignant. Landouski[2] also quotes a case of Modrzejewski's in which a large subcutaneous tumor in the region of the left clavicle underwent sarcomatous degeneration, followed by ulceration and gangrene and causing the death of the patient.

Xavier Delore[3] quotes a case of Professor Poncet in which an enormous sub-aponeurotic sarcoma developed in one of the thighs of a patient suffering from generalised neurofibromatosis, necessitating the amputation of the limb.

1. Cimmino. loc. cit.
2. Landouski. loc. cit. p.57.
3. Xavier Delore. Gaz. des Hop. 28 April 1896.

Professor Blüm[1] also in a case of the same disease quoted by Feindel removed the right thigh for a sarcoma of that limb.

We remember that von Recklinghausen in his report on the Autopsy of Marie Kuntz expressed his belief that certain nodules found on the intestines were neurofibromata which had undergone sarcomatous degeneration.

The prognosis will of course depend upon all these circumstances; the disease may be dormant for a long time, but when it is set into activity it follows a slow though steady course and sooner or later the patient succumbs either to the exhaustion caused by the disease itself or to some of the numerous complications to which his condition is liable.

In the diagnosis of the disease, first of all the history should be taken into consideration. Where we get multiple cutaneous tumors coming on early in life and accompanied by pigmentation of the skin there can be little doubt of the disease, especially if subcutaneous tumors as well are made out along the line of the nerves.

1. Feindel. loc. cit. p.70.

Where the disease comes on late in life, it may be necessary to distinguish the growths from syphilitic gummata, but here again the history will help and a hint as to an effective manner of clearing up the diagnosis is given by Lebourecq[1] who reports a case of neuroma (sic) which disappeared under treatment with Iodide of Potassium. Multiple fatty tumors are those which are most apt to be confounded with neurofibromata. Alsberg[2] who has published a dissertation on the subject came to the following conclusions. "That there are lipomata which arise from the connective tissue sheaths of the peripheral nerves and thus belong to the group of the pseudo-neuromata; that these neurolipomata are allied to neurofibromata as much from a clinical as from a histologic standpoint and that it looks as if a certain number of symmetrical and congenital lipomata should be enumerated among the ranks of neurofibromata".

The same writer quotes notably a case of cruveilhier in which the latter's description of certain multiple lipomata could in the absence of a histological examination well pass for neurofibromata. It

1. Ashurst. The international encyclopaedia of Surgery. Vol.III. p.600.
2. Alsberg. Ueber neurolipome. Berliner Inaugaral Dissertation. 1892.

will be remembered that we referred to a similar case published by Claus.

In ordinary cases of multiple lipomata though the feel of the tumors is very like that of the neurofibromata and the other tumors of the skin, yet the former are generally flatter and do not project from the surface even when of considerable size in the way that the neurofibromata and other tumors do in generalised neurofibromatosis. In Guillaume's case, we remember there were several large lipomata or at any rate tumors which gave the impression of being of that nature, which were hardly visible on the surface of the skin. Moreover multiple lipomata are usually lobulated and rarely pedunculated. Where the other signs of the disease are present such as pigmentation and the small dermato fibromata fatty tumors are not so apt to be confounded with neuro-fibromata. The presence of vascular and piliary naevi should also be looked for.

Von Recklinghausen we remember pointed out a resemblance between Leprosy and generalised neuro-fibromatosis, but the pigmentation in leprosy is quite unlike that of the disease we are dealing with, it is

more in the form of blotches and patches of discolouration than of the "coffee and milk" and brownish red sharply defined spots we find in generalised neurofibromatosis. Landouski points out also, that in leprosy the discoloration is of a deeper tint in the centre than towards the periphery while, as we know in generalised neurofibromatosis the spots and patches are uniform in their color and their bodies are sharply defined from the surrounding skin.

In tubercular leprosy the nodules are altogether unlike our dermato fibromata, they tend to run together in irregular lumps and have a swollen oedematous appearance, like large pomphi inurticaria; in fact I have personally known a case where a certain family was thrown into the greatest state of consternation at the fate of their son who had suddenly developed an urticaria which they took to be leprosy. Altogether I do not think there is much possibility of mistaking the lesions of generalised neurofibromatosis for those of leprosy or <u>irce verva</u>.

In the cases which come on late in life, disseminated cancer of the skin may be mistaken for neurofibromata. The history and the microscope will clear

up the diagnosis. In advanced cases the peculiar cachexia of the disease will greatly assist the diagnosis.

The disorders of cutaneous sensibility, the mental state, the general passivity are all points to be looked for and noted.

Such then are a few of the principal facts in connection with certain aspects of generalised neurofibromatosis.

We have yet to view the disease under other conditions which are perhaps still more interesting than those we have past studied.

PLEXIFORM NEUROFIBROMA.

It will be remembered that reference was made to a case of generalised neurofibromatosis observed by Herczel in which the patient Susy Merschel, in addition to other lesions presented an extensive elephantiasis-like growth on her left arm; this growth we also recollect was referred to as belonging to the class of plexiform neuromata, and it is of the latter that we now propose to give a few details. The term plexiform neuroma which as we shall have occasion to

show is an incorrect one, was adopted by Verneuil who had studied two cases, one in connection with Depaul in 1857, and the other with Guersaut in 1859, and includes a variety of morbid conditions of the skin and subcutaneous tissues. These affections which often include small multiple dermato fibromata and pigmentation of the skin, usually take the form of large tumors varying in shape and appearance, and situated on various parts of the body, but more frequently about the cephatic extremity. They have been recorded as far back as 1808 by John Bell[1] and later in 1832 by Alibert[2] and have received various designations according to the characters presented by different cases. Thus we find in 1854 before Verneuil had made his observations Dr. Valentine Mott[3], who at that time was Emeritus Professor of Surgery in the University of New York publishing five cases of this condition, under the name of Pachydermatocele, a term which it will be observed involves some confusion since it is also applied to Elephantiasis Arabum.

1. John Bell. Principles of Surgery, 1808, Vol.III.
2. Alibert. Monographic des Dermatoses. Paris 1832.
3. Valentine Mott. Remarks on a peculiar form of tumor of the skin denominated Pachydermatocele Med. chiv. Wans. 1854. Vol.37. p.155.

Dermatolysis is another term which has been employed in connection with the condition but though it sounds learned enough, of course it merely means "lax skin" and can hardly be regarded in any other light than that of a popular term designating a particular aspect of plexiform neurofibroma. The denomination congenital elephantiasis used by several authors, describes the mode of origin and the microscopic character of another's aspect of the condition, without giving any indication of its anatomo-pathological character. In the name "molluscum elephantiasique" adopted by Nelaton, we have the first approach to the proper terminology of the condition, but it is to Bruns[1] who had the opportunity of observing eight cases, and who published two works on the subject, one in 1870 and the other in 1891, that we owe the best designation the condition has received. He suggested two names "Rankenneurom" and "Neurofibroma Cirsoideum". Either of these he thought should be used in preference to Verneuil's denomination of Plexiform neuroma, because he had observed that the

1. Bruns. Ueber das Rankenneurom. Archiv. f. Klin. Chiv. t.XLII.

nerves involved in the growths concerned were not arranged in the manner of a plexus, but rather had the appearance of a Varicocele or of a Cirsoid Aneurism. But strangely enough "Rankenneurom" (Racemore neuroma as Norman Walker translates the term) and "Neurofibroma Cir soideum" are not interchangeable terms. The histology of the growths do not permit the use of the term "neuroma" at all, there being no increase of nerve tissue in the nerves implicated, while "neurofibroma" accurately represents the true condition. The latter is therefore the more correct of the two terms. As to Verneuil's terminology, it is doubly wrong; first as regards the word "plexiform" as Bruns has shown, and lastly as regards the term "neuroma". As the disease, however, has been long known under the designation of plexiform neuroma, it will perhaps tend to produce less confusion if we retain the word plexiform and merely alter the neuroma to neurofibroma; hence throughout the rest of this paper the disease shall be designated plexiform neurofibroma.

The multiplicity of names under which the condition is described indicates to us that the latter

Opposite Page 158.

Fig.XX. Case of congenital plexiform neurofibroma of elephantiasis type. After Max Jordan.

may assume a variety of forms. The chief of these are.-

1. Diffuse cutaneous hypertrophy resembling elephantiasis. (congenital elephantiasis).

2. Large cutaneous tumors of indefinite shapes. (Pachydermatocele).

3. Cutaneous tumors forming overlapping folds. (Fibroma pendulum. Pachydermatocele).

4. A condition of laxity of the skin without marked hypertrophy. (Elastic Skin. Dermatolysis.)

In the first form mentioned the condition is that of a diffuse hypertrophy of the skin and subcutaneous tissues. The surface of the growth is usually pigmented and rough or thrown into folds. The resemblance to an elephant's hide from which it receives its denomination is very precise. As is the case with the other forms under which the condition is met, this elephantiasis-like growth is frequently accompanied by the commoner lesions of generalised neurofibromatosis. We remember the case of Herczel, already quoted, where the patient Susy Merschel had an extensive hypertrophy of the external aspect of the left arm. The surface of the growth was diffusely pigmented,

rough, and rugose like the hide of an elephant.

Crocker[1] quotes a remarkable case of this kind shown by Mr. Treves in 1885 before the Pathological Society of London. The patient was a man who used to exhibit himself at shows as an "elephant man". According to Crocker the bulk of the disease was on the right side; there was enormous hypertrophy of the skin of the whole right arm measuring 12 inches round the wrist and five around one of the fingers. A lax mass of pendulous skin etc. depended from the right pectoral region. The right side of the face was enormously thickened and in addition there were huge unsymmetrical exostoses on the forehead and occiput. There were also tumors affecting the right side of the gums and palate, on both legs but chiefly the right, and over nearly the whole of the back and buttocks. The skin was immensely thickened with irregular lobulated masses of confluent tumors, presenting the ordinary molluscum characters. The 6 ft. arm and hand were small and well formed. The man was 25 years old, of stunted growth and had a right talipes equinus, but was fairly intelligent. The disease

1. Crocker. (H.Radcliffe) Diseases of the skin. 2nd. Edition.

was not perceived much at birth but began to develop when patient was five years old, and had gradually increased since. "Of course" says Dr. Crocker in conclusion "it was ascribed to maternal fright".

In regard to the second form mentioned in the list, the tumors are found in any part of the body, but the cephalic extremity, especially in the neighbourhood of the superior eyelids is a favourite seat of origin. The growths are irregular in shape and usually the surface is smooth though not infrequently rugose even to the extent of forming small folds. As in the preceding condition their surfaces tend to be pigmented, in fact in some cases they are observed to take their origin from a pigmented mole.

Andry and Lacroix[1] have observed that those occurring on the trunks and limbs are more frequently pigmented than those on the face. In many cases they are covered with soft downy hairs.

We remember one of Czerny's Cases already quoted, the patient had an enormous tumor on his back.

1. Andry et Lacroix. Les nevromes plexiforms et les Pachydermies nevromateuses. Lyon medicale 1891.

This growth on examination proved to be a plexiform neurofibroma. Professor Kosinski of Warsaw operated on the case of a woman F.K. aet 27, who had a similar tumour of great volume depending from her sacro-lumbar region. A similar case was operated upon by Dr. Gustavus Fritsche[1] and a tumour weighing 35 lbs was removed. In a communication to the Clinical Society of London (read by Tilbury Fox) Fritsche drew attention to the fact that his was the fifth case in which the removal of a tumour of such large dimensions had been recorded in medical literature.

The first, described by Virchow, weighed 32½ lbs. The second, a scrotal tumour, extirpated by Liston weighed 40 lbs. The third, by Professor Kitter of St. Petersburg, and the fourth operated upon by Bickerstelt of Liverpool weighed 32 lbs.

Feindel[2] quotes a case of M.Follemer in which a man C.H., aet 33, had a large plexiform neuroma on the posterior aspect of his head. A case shewn by M.Collet before the Medical Society of Lyons is published[3] in which the patient had a large plexiform

1. Gustavus Fritsche. Clin.Soc.Trans. 1875,Vol.iii. p.158.
2. Feindel. loc.cit. p.64.
3. Nevrome plexiforme. Gaz. des Hop. de Toulonne, 1893. p. 45.

Opposite Page 162.

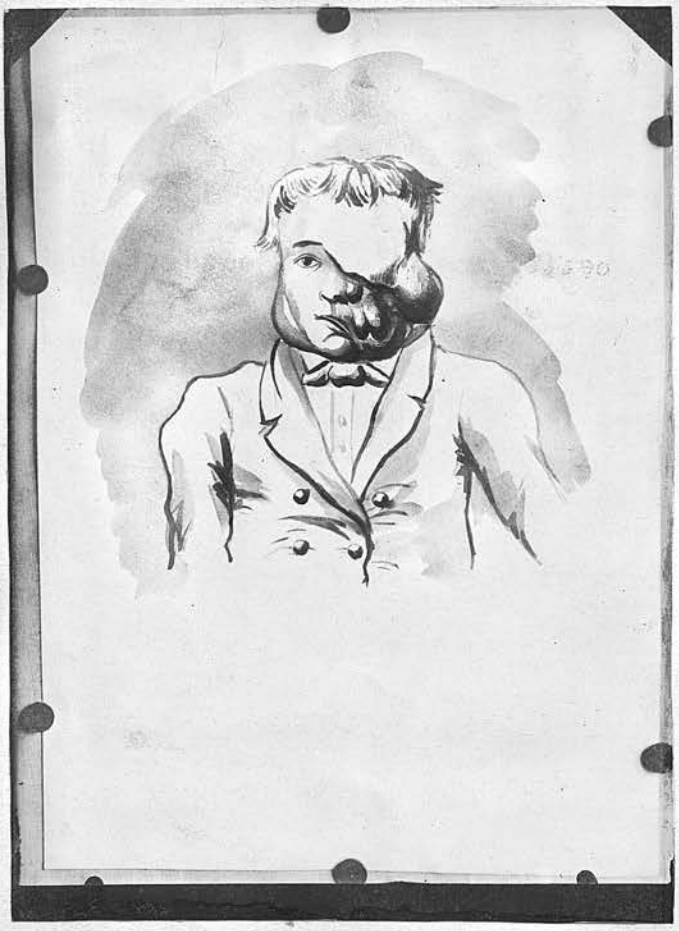


Fig.XXI. A.R. Case of congenital plexiform neurofibroma of "Fibroma Pendulum" type after Valentine Mott.

neurofibroma extending from the tragus of the right ear to the chin on the same side.

The third form mentioned in the list is one of the most interesting. The growth starting from some fixed point on the face or head forms huge elongated dough-like masses of hypertrophied skin, which lie superimposed on each other in the manner of the convolutions of a coachman's cape. A reference to the accompanying photograph of Mott's and Wright's cases will better explain the condition than any words can. Of the five cases communicated by Mott I quote here the two whose portraits accompanied the monograph as being really most remarkable instances of this form of the disease.

The first is the case of "A.R. a boy, aet 14, of sound constitution who consulted about a hideous deformity of one entire half of his head and face. It consisted of three layers of tumours from the crown of the head to some distance below the base of the jaw. One of them was formed in or involved the eyelids which were carried down to the lower part of the face; when this portion was raised up the ball

Opposite Page 164.

Fig.XXII. Miss S. Case of congenital plexiform neurofibroma of "Fibroma Pendulum" type after Valentine Mott.

The next case of Mott is that of "an unmarried woman, Miss "., aet 24, of robust country health. The tumours were of a dark brown or coppery colour, soft, with an elastic feel, like a collapsed lung or a placenta. The tumours hung in beautiful and fantastic folds like the convolutions of a tippet over the neck, shoulders and chest. There were five of these folds or stories, the smallest above and the largest or broadest below. It was attached to the healthy integument behind and in front of the ear directly under the lobes, to the entire extent of the side of the neck from near the nucha to the edge of the larynx and trachea to the whole line of the clavicle and the middle and upper segment of the sternum, over the shoulders, part of the scapula reaching upon the arm to near the insertion of the deltiod, over the entire pertoralis major to the middle of the sternum and ensiform cartilage and to the upper part of the rectus abdominis and latissmus dorsi with a part of the serratus magnus. Length , 21 inches, breadth 18 inches."

Opposite Page 165.

Fig.XXIII. Case of generalised neurofibromatosis with enormous dermatofibroma becoming pendulous on acount of its great weight - after Tappey.

Such were these two most extraordinary cases whose portraits I have reproduced.

Dr. Marie warns those interested not to confound this condition with that in which a large neurofibroma of the molluscum type drags down by its weight the skin on which it is implanted, thereby becoming more or less pendulous as in a case published in 1889 by Tappey[1].

Dr. Wright[2] has published a case similar to those of Mott described above. It was that of a woman Sarah H., aet 34, who was admitted into the West Riding County Asylum in October 1864. A portrait of this case is also here presented.

These cases are not very common, but they crop up from time to time and records of them are scattered

1. Tappey, Journ. of Cutaneous and genito Urinary Disease, 1889.

2. Wright. Henry G. Path. Soc. Trans. Lond., Vol 16. p.270.

Opposite Page 165a.

Fig.XXIV. Sarah H. Case of Plexiform Neurofibroma of "Fibroma Pendulum" Type after Wright.

about the medical journals.

The next form under which the disease is sometimes seen is that to which the name Dermatolysis should be restricted; the skin becomes very loose, as if there was a disconnection between it and the sub-cutaneous tissue permitting the former to be freely drawn in every direction. Such cases have been observed for several centuries. Crocker records that in 1657 a young Spaniard named Georgius Albes used to draw the skin of the right pectoral region over to the left ear and the skin under the chin over the face to the vertex. The skin over the knee could be extended half a yard and when the tension was taken off it retracted to its normal situation without being thrown into folds. This mobility was limited to the right side.

In 1882 an "elastic skin man" was exhibited at the Royal Aquarium in London, and in 1892 most of us who lived in Edinburgh had the opportunity of seeing a similar'wonder'in the Christmas Carnival at the Waverley Market. In these cases the skin does not undergo any marked hypertrophy. This condition must

be distinguished from that found in some multiparae in whom the skin over the abdomen becomes very loose, but, of course, the other signs of generalised neurofibromatosis, such as pigment and dermato-fibromata are wanting. Lax skin is also observed in old age especially among people who have been very fat.

The principal seat of election of plexiform neurofibromata is the cephalic extremity. Bruns, who has published statistics of 30 cases, 8 of which were from personal observation, distributed them as follows

15 cases starting from the upper eyelids.

8 cases from the posterior auricular region and from the back of the neck.

3 cases from the nose and cheeks.

On the trunk the condition is much less frequent and still less so on the limbs.

Plexiform neurofibromata in its principal aspects is most usually congenital.

If the growth be not actually present at birth, it makes its appearance very early in life and usually starts from a pigmented mole or a naevus or from the site of some small tumour in the skin. The five

cases communicated by Mott were all congenital. The hereditary element is also commonly out. In M.Collet's case already quoted the patient's mother presented the typical pigmentation of generalised neurofibromatosis upon her body.

Bruns[1] has recorded the case of a man, aet 18, who had a large plexiform neurofibroma 18 centimetres in diameter on his back. This patient's paternal grandfather and his (patient's) three brothers also presented smaller growths of the same nature on their skin. His mother and his sister were free from the disease.

At a meeting of the Medical Society of Berlin on June 26th, 1895, M.James Israel exhibited two cases of plexiform neurofibroma. In one case the nervous connection was manifested in that the patient's father was an epileptic; in the other a sister and a cousin of the patient were also suffering from plexiform neurofibromata.

Sometimes there is a history of the disease following upon a traumatism as in the case of C.H.

1. Bruns. loc.cit. p.584.

quoted by Feindel[1] in which the mother of the patient ascribes the origin of a large plexiform neurofibroma on the back of the latter's head to a fall which he had at the age of two or three.

An injury, however, may only cause the more rapid growth of a pre-existing tumor as was clearly observed in the case of M. Collet already quoted where the patient aet 19 had a slowly growing tumor from birth, which after one day being irritated by a blow from a wooden shoe suddenly took on a rapid growth and greatly increased in size in the space of a month, after which it resumed its former indolence.

Very commonly the ordinary features of generalised neurofibromatosis are present along with plexiform neurofibromata.

Bruns[2] states that in most cases, pigmentary spots at any rate are present in greater or less numbers in various parts of the body.

He is of opinion that there is a common genesis for a certain class of fibromata. He comprises the latter under the universal denomination of elephant-

1. Feindel. loc. cit. p.29.
2. Bruns. loc. cit. pp.588-9

iasis nervorium. When the degeneration attacks generally the nerve trunks the condition is designated as generalised neurofibroma; and plexiform neurofibroma where it is localised to the nerve branches of a circumscribed nervous territory. When the growths are on the extremities of the cutaneous nerves they are designated fibromata mollusca; but the entire process is the same; the difference in the clinical aspects is merely due to the difference in the anatomical character of the parts involved. Besides the cases in which cutaneous pigmentation alone accompany the condition of plexiform neurofibromata, Bruns[1] refers to an instance where there were not only present the characteristic spots and patches, but also large numbers of subcutaneous nodosities along the line of the nerves.

We recollect that Susy Merschel whom we have so often referred to, had in addition to a plexiform neurofibroma of the elephantiasis-like variety, the typical dermato fibromata and pigmentation for generalised neurofibromatosis.

In Czerny's case, also referred to on a previous

1. Bruns. loc. cit. p.584.

occasion; the following combination was present.-

An enormous plexiform neurofibroma on the back; numerous dermato-fibromata, and several subcutaneous nodules along the line of the nerves.

These references are sufficient to show that this condition of plexiform neurofibromatosis which has hitherto been looked upon as a separate disease is frequently, indeed almost constantly found in association with the well known features of generalised neurofibromatosis. All the clinical evidence goes to show that the various forms of plexiform neurofibroma are merely varieties in the expression of these common morbid process peculiar to generalised neurofibromatosis.

And not only clinically but pathologically as well we find the two processes essentially the same.

According to Bruns, to the touch these tumors are of unequal consistency. Within their depths are felt hard nodules and numerous cylindrical structures like bits of thick string which can be made to move over one another.'

The naked eye appearances of the tumors immediately after extirpation exhibit special structures

Opposite Page 171.

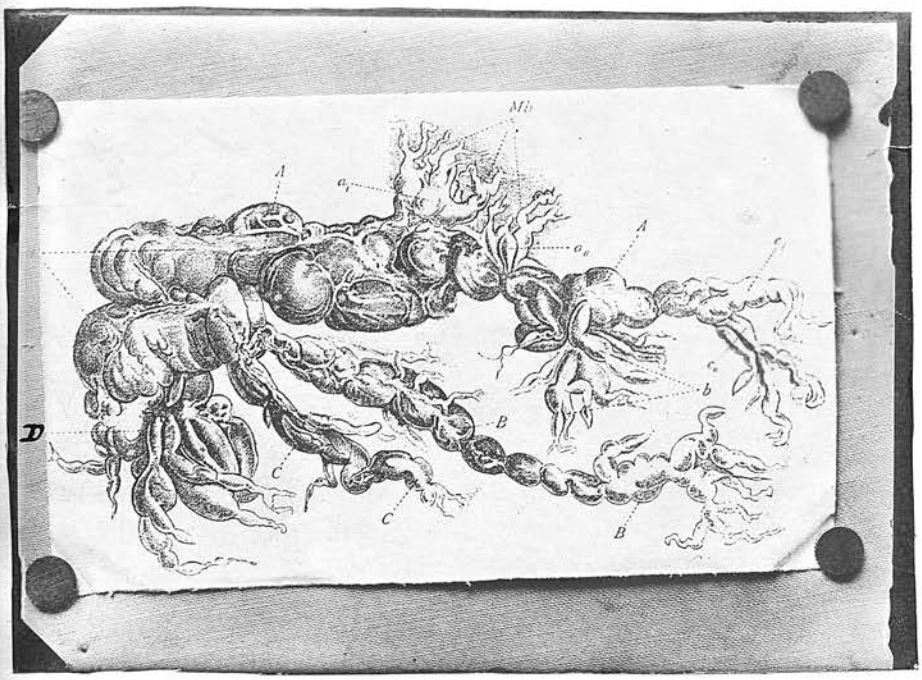


Fig.XXV. Pleviform neurofibroma of left Brachial plexus dissected out.
A. Musculocutaneous nerve. a.a. twigs to Biceps. b. twigs to Brachiatis Anticus.
B. Internal-cutaneous nerve. After Herczel.

imbedded in a matrix of soft succulent, vascular, reddish connective tissue; these special structures are yellowish white cylinders twisted and folded on themselves in the most intricate manner and bearing nodosities on several points in their distribution. Andry and Lacroix[1] who have studied the condition very closely thus describe the naked eye appearance of a section through a plexiform neurofibroma.-

"We find in the deep layers of the skin and in the subcutaneous cellular tissue a network of white or yellowish white cords of large calibre mixed and tangled up, and anastomosing with each other in the most irregular and intricate manner. They are hard, dry, and elastic and present to some extent the appearance of half cooked macaronis. Moreover they they have no central lumen and are formed by a compact white tissue. Their cut surface is not plane, but presents a bulge at the centre as if the external layers of the cylinders retracted themselves after section. They are all pressed together and bound up in a delicate looking and sometimes vascular connective tissue".

1. Andry et Lacroix. loc. cit. p.146.

More recently, however, M. Darier has furnished us with a very complete report of the microscopic and microscopic examination of a plexiform neurofibroma made for M. Delens and quoted by Feindel[1]. This report is very instructive and I reproduce it here below.-

"Microscopic Examination. A bundle of nerves appearing to be the branches of a single nerve trunk is seen to start from one corner of the specimen. These branches are hypertrophied, tortuous, varicose and moniliform; they present a swollen appearance, the largest being about the size of a medium nerve; they are twisted upon themselves in figures of five or in spirals, and are thus both thickened and elongated. On account of their numbers these branches are almost in contact with each other and they are united by a very resistant fibrous tissue which renders their dissection extremely laborious.

Feeling them through the Matrix in which they are thus bound up they yield to the touch the sensation of knotted and tangled cords. These nerve cords in dividing themselves into smaller branches reach nearly

1. Feindel. loc. cit. p.37.

up to the skin where they are lost in the midst of dense fibrous tissue, for the skin itself is the seat of a very pronounced fibrous hypertrophy. The smaller branches of the nerves are really not very fine; they still retain a considerable size and are varicose and tortuous.

In the recent state the cut surface of the tumor is bluish white and moist, and of a leathery consistency.

The Histological Examination was made on the swollen and tortuous nerves both in cross section and in longitudinal section, and also in bits of skin removed from parts in contact with the diseased nerves. The specimens prepared by the use of Osmic Acid gave the best results.

A. Taking the transverse sections of the nerves as our first type, we found that it was composed of two bundles, each one being isolated by its lamellar sheath. This lamellar sheath is very distinct although the layers which go to make it up are in some places separated from each other for a little distance by a connective tissue which has insinuated

itself between them. In the midst of this connective tissue are seen the myeline cylinders of transversely cut nerves grouped together so that far from being directly applied to bundles of nerve cylinders the lamellar sheath is separated from them by a dense layer of newly formed connective tissue. The total diameter of the nerve bundle is on this account increased at least ten times. The nerve cylinders grouped together in the centre of the bundle seemed normal, both when viewed in longitudinal section; and when the latter hit exactly the central axis of the nerve bundle it is possible to follow the myelin cylinder for a good distance, and to observe some annular constrictions on its course. There are no degenerated nerve cylinders, nor is there an appreciable quantity of nerves in any way damaged by the growth of fibrous tissue. This tissue which separates the nerve bundles is almost entirely composed of longitudinal fibres which is the general rule in all the cases examined.

The newly formed connective tissue which fills the rest of the space comprised in the interior of the lamellar sheath is on the contrary composed of

wavy bundles interlaced in every possible manner and in the midst of which are seen numerous connective tissue corpuscles, blood vessels, and a few stray nerve cylinders.

No elastic fibres are observed. This there is evidently a new formation of fibrous tissue rich in connective tissue corpuscles, situated in the interior of the nerve bundles; that is to say an intrafascicular fibroma of the nerve, while there is nothing which indicates a new formation of nervous tissue or in one word, a neuroma.

Outside of the lamellar sheath there is an evidently newly formed fibrous tissue which binds the nerve bundles to one another, and to neighbouring structures; it is dense, and composed of fibres intermixed with numerous connective tissue corpuscles; its presence explains the difficulty of dissecting out the nerves.

We have therefore, both an intrafascicular and an extrafascicular fibroma.

B. In examining the sections of skin, the following facts are made out.-

The epidermis and the papillary body show no abnormality, but in the region of the true skin the normal aspect is not seen. The corium is infiltrated or replaced by a tissue which calls to mind a diffuse fibroma. It is a dense, compact networking of frail fibres pointing in every direction, and mixed with numerous connective tissue cells, a few round cells, and also some granular ones. (Mast Zellen). The elastic fibres of the normal tissue are present. The hair follicles are imbedded in the matrix of the fibroma, and so also are the sebaceous and coil glands and the blood-vessels. These various organs are not altered in structure, but their adventia is continuous with the surrounding connective tissue. Lymphatic channels are scarce in the newly formed growths.

The condensation of the tissue is seen even more clearly in the deep layers of the corium and in the subcutaneous layers where the appearance of a diffuse fibroma is more marked.

The fat lobules are choked and dissociated by the fibrous new formation. Large vessels and nerves are seen in the thick strands of fibrous tissue which separate the fat lobules.

The nerves are the organs which present the most characteristic lesions. Here also as in those of a larger calibre previously described, fibroma tissue is found in the interior of the lamellar sheaths and the bundle of nerve cylinders lie in the centre of the former. The size of the nerves is increased to six or eight times their normal. All the nerves met with in the skin are in this same condition. It is only quite close to their endings in the neighbourhood of the papillary bodies that the intrafascicular fibrous newformation seems to cease. The conclusion to be drawn from this analysis is that the dominant feature in this case is a fibrous newformation the seat of which is moreespecially in the interior of the lamellar sheath of the nerves. It is a question, therefore, not of true neuroma but of a fibroneuroma of the nerves and there is besides a diffuse fibroma of the skin.

We know von Recklinghausen's theory on the subject of this habitual coincidence of pseudo neuromata or fibromata of nerves and multiple fibromata of the skin. Whatever may be the value of the explanation which he has given to this fact it seems that

in the present case we have to do with the affection that he has described namely with neurofibromata.

I have to add the presence in this case of multiple naevi and pigmentary spots of different sizes on the thorax and on the arms. This coexistence is the rule, although the reason is not known".

From the foregoing report we have further proof that this condition of plexiform neurofibromatosis is essentially the same process as we have studied in relation to the other forms of generalised neurofibromatosis. Instead of the connective tissue hyperplasia manifesting itself in the formation of multiple dermato fibromata scattered all over the body, the growth is circumscribed and limited to a certain area at least this is true for the principal tumors, for in addition to it we almost constantly find a few small dermato fibromata scattered here and there over the body. As regards the nerves in plexiform neurofibroma, instead of a discrete formation of fibrous tumors along the course of the subcutaneous and other nerves, we have a general increase of the connective tissue sheath of adjacent herve

trunks in a circumscribed nervous territory in which the nerves involved are all matted together in the general mass of newly formed connective tissue. At the points where these nerves cross each other in the general meshwork formed by their interlacement, nodosities are seen which according to Dr. Arnorzan[1] present a special structure. In a paper read before the "Congress for the Advancement of the Sciences" on September 18th. 1892, he stated the following.-

The hypertrophied or newly formed nerve cords which constitute plexiform neuromata have been the objects of precise study. The nodosities which are found at the points where they cross each other, have been passed in silence by the majority of authors and only mentioned by the rest under the name of neuroma, and perhaps even confounded sometimes with lymphatic glands. In two cases of plexiform neuroma a histological study of these nodosities has shown me that they are true nerve ganglions having an abnormal function. The first case bears reference to a woman

1. Dr. X. Arnorzan. Ganglion nerveux de formation pathologique dans le nevrome plexiforme. Congres pour l'advancement des Sciences. Seance du 18 Septembre 1892. (matin).

aet 36 inwwhom the tumors present were of such enormous volume and weight, as to bring about the spontaneous luxation of the superior cervical vertebrae, entailing a lateral compression of the spinal cord and complex nervous manifestations such as hemianaesthesia, crossed hyperaesthesia etc. The second case is that of a young girl aet 15 in whom the tumor was implanted on the occipital region, and removed surgically. In both cases the tumors presented the classical characters of plexiform neuromata. The nodosities referred to, had the following structure.-

Sheath fibrous, stroma fibrous, nerve cords cut in different ways, according to the direction in which they traversed the nodosity, and lastly large nerve cells, each one being encapsuled in a little connective tissue compartment, provided on its internal surface with a layer of endothelial cells. Thus constituted, these nodosities really have the structure of the intervertebral ganglia of the dorsal region the only point of distinction between them and the latter is their larger volume and the presence of embryonic blood vessels in their thickness".

Meslet[1] who has contributed to the subject quotes Arnozan especially with reference to three cases published by the latter in 1892[2].

Arnozan makes no suggestion as to what the abnormal function of these ganglia may be.

Returning to the general features of plexiform neurofibroma, we remember that the pigmentary spots and the typical dermato fibromata of the commoner cases of generalised neurofibromatosis are frequently met with in the former condition, and even the nodules on the subcutaneous nerve trunks may also be present, as we have seen in Czerny's case.

In tracing the various forms of plexiform neurofibroma to their origin we find that they occur indiscriminately in the same family where one member may present the characteristics of plexiform neurofibroma, while in another the more ordinary signs of generalised neurofibromatosis are evidenced. An even more striking fact is that a parent presenting the tumors and spots and other symptoms of generalised neurofibromatosis may give birth to a child exhibiting

1. Meslet. Contribution a l'etude de nevromes plexiformes These de Bordeaux, 1892.
2. Arnozan Recueil d'Observations de Dermatologie Bordeaux, 1892.

the signs of plexiform neurofibroma in any of its varieties. A notable example of this being the case of the Merschel family in which the mother Mrs. Merschel herself suffering from generalised neurofibromatosis gave birth to a child exhibiting a plexiform neurofibroma of the elephantiasis type.

The association of plexiform neurofibroma has been recognised by Unna[1] who states that "neurofibromata are frequently accompanied by plexiform neuromata of the cutaneous nerves and nerve trunks", and further on he goes on to say that "neurofibromata occasionally appear alone but are often accompanied by other forms of congenital tumors, naevi pigmented moles, angiomata, patchy dermatocele, and other forms of congenital elephantiasis.

It is therefore, with good reason that all these apparently different processes including the pigmentation of the skin, in spots and in patches, and sometimes diffusely, the formation of multiple dermato fibromata some of which are merely simple hyperplasias of the connective tissue of the skin, while others are connected with the cutaneous nerve terminations tumors

1. Unna. loc. cit. article, p.844.

along the course of the subcutaneous nerves, diffuse hypertrophy of a portion of the skin with hyperplasia of the connective tissue of the nerve trunks in the territory involved with matting together of the nerves, and the various nervous and other disturbances already dwelt upon, have been grouped by Dr. Marie under the heading of generalised neurofibromatosis.

In regard to treatment, there is very little to be said. It must be mainly symptomatic.

In one of Payne's[1] cases the neuralgic pains were relieved by Quinine and Iron, and indeed the general condition of the patient improved and the tumors ceased to increase in number, while several already existing ones grew smaller and finally disappeared, but Dr. Payne is careful to mention that he did not in any way attribute the improvement to his treatment.

Where the disease chiefly expresses itself in the formation of large plexiform neurofibromata or large simple neurofibromata, surgical interference may be resorted to and the entire tumor extirpated.

Mott operated on the five cases which came under his observations; they were as follows.-

1.J.F.Payne. Trans.Path.Soc.Lond. Vol.38, p.69.

1. female aet 24.
2. " " 40.
3. boy " 14.
4. " " 12.
5. man " 45.

In three of the cases there was no disposition to the return of the growth after excision. Of the two in which the growth returned, one was that of the boy A. R. whose portrait we give here.

Speaking of his condition Mott says "a few weeks afterwards (after the operation) there was a renewal of the growth. He wasagain operated upon. In less than a year the growth renewed itself and patient once more rendered hideous".

Besides these cases of Mott we have already referred to large growths of the kind removed by Professor Kosinski of Warsaw and by Dr. Gustavus Fritsche of Czenstochowa in Poland, and others. The tumors are usually very vascular the vessels being of large size and the haemorrhage difficult to control.

M.M. Ramakers et Vincent[1] give statistics of 29 cases operated upon by different surgeons with 5 deaths caused as follows.-

1. Ramakers et Vincent. Archiv. provinc. de chivurg. Aout. 1894.

One by Pyaemia (Czerny).

One by Gangrene (Winiwarter). In this case the arm was disarticulated at the shoulder. P.M. The presence of sarcomata was made out in the lungs.

One by cerebro spinal meningitis (Chavasse). In this case there were plexiform neuromata of the branches of the cervical & dorsal nerves.

One by chronic septicaemia (Arnozan) and the last

One by Odema of the glottis (Ourry).

In one instance there was an immediate return of the disease (second case of Christol) and in another instance the return was a little delayed (first case of Arnozan) but even where the interference was only partial a complete and permanent cure was frequently obtained.

Such then are some of the principal facts in connection with this most interesting group of phenomena described under the title of Generalised Neurofibromatosis.

Owing to the diffuse manner in which these facts are scattered throughout the medical journals, and in monographs, essays and other works difficult to access, the task of collecting them has been a very laborious one, the more especially as the texts invol-

ved at least three languages, two of which had to be rendered into English.

In my search for information I consulted the libraries of the Royal College of Physicians, Edinburgh, The Royal College of Surgeons, London, the British Museum, the British Medical Association London, where by the way I found Dr. Marie's book uncut, and the Medical Library of the University of Paris.

I am endebted to M. Marie for several cuttings taken from various journals and having reference to the disease.

I am glad to have this opportunity of expressing my deep sense of recognition of M. Marie's great kindness and affability to me as a student of the Edinburgh University. It is to him I owe my first acquaintanceship with this remarkable disease which, speaking as one who has but recently left the University benches, is practically unknown to the average student, and indeed to the average graduate as well. Only as late as last year in a review of Dr. Marie's Book, we find M. Launois[1] thus expressing himself

1. M. Launois. Revue de livres. Lyons Medicale 1896. No.81. p.551.

"enfin la derniere et tres interessante leçon est consacrée a l'étude de cette affection encore mal connue du public médicale, la neurofibromatose généralisée".

It is also to Dr. Marie that I owe the facility for studying the case of Flond which has formed the foundation of this work, and I can confidently say that without his kind encouragement and the amiable manner in which he was always willing to discuss with me the subject of generalised neurofibromatosis, this thesis would never have been written.

The text is illustrated by 25 photographs of cases and anatomical specimens bearing upon the disease. Some of the photographs were taken by myself, others from plates kindly given to me by M. Marie, and the rest from drawings which I engaged an artist to execute from sketches made by myself, in cases where access to the works in which the original drawings appeared, was restricted. The artist has done his work very satisfactorily and the reproductions are very faithful considering the circumstances under which they were done.

I have also had 29 lantern slides prepared from my negatives. As I spared no pains to get them properly executed and at considerable expense, I trust I may venture to hope that some use may be found for them.

In conclusion I can only beg to commend this humble work to the consideration of my examiners.